Three dimensional (3D) ultrasonography in uterine disorders

Nieuwenhuis, L.L.

2017

document version
Publisher's PDF, also known as Version of record

THREE DIMENSIONAL

ultrasonography in uterine disorders

LOTTE LISA NIEUWENHUIS

Cover design & layout
Design Your Thesis | www.designyourthesis.com

Printing
Ridderprint | www.ridderprint.nl

ISBN 978-94-6299-767-7

VRIJE UNIVERSITEIT

Three dimensional (3D) ultrasonography in uterine disorders

ACADEMISCH PROEFSCHRIFT

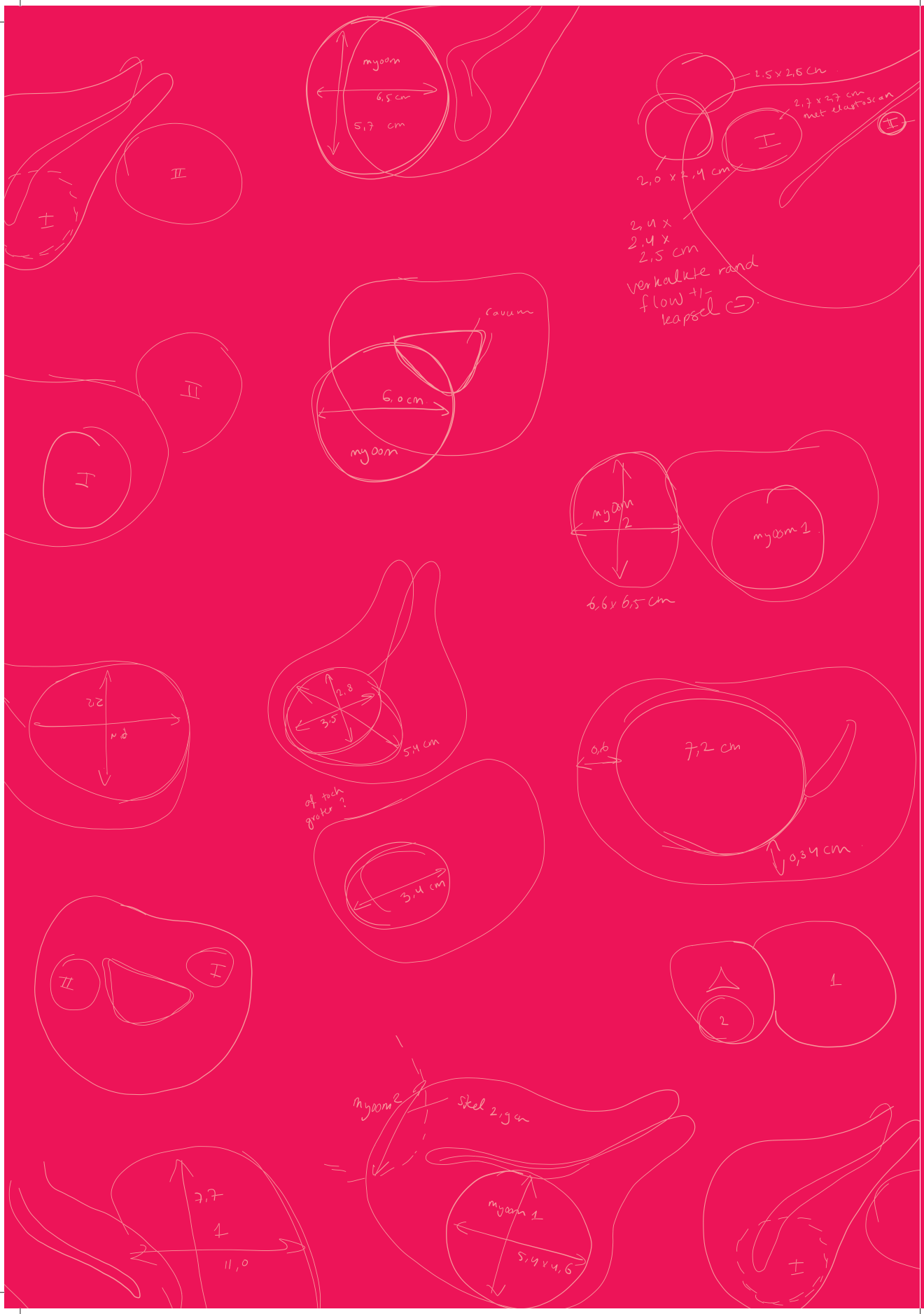
ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Geneeskunde
op dinsdag 21 november 2017 om 9.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Lotte Lisa Nieuwenhuis
geboren te Maputo, Mozambique

promotoren:	prof.dr. J.A.F. Huirne prof.dr. H.A.M. Brölmann
copromotoren:	dr. W.F.K. Hehenkamp dr. W.M. van Baal

TABLE OF CONTENTS


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
1
myoom 2
stiel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

01

General introduction

GENERAL INTRODUCTION

Polyps and fibroids

Pathology can be found trough all three layers of the uterus; the endometrium, myometrium and serosa. In this thesis we will focus on the most common abnormalities of the uterus; fibroids and intracavitary abnormalities such as polyps. These benign abnormalities can cause several complaints including abnormal uterine bleeding (AUB) and subfertility. Polyps are focal abnormalities within the uterine cavity arising from the endometrium. Leiomyomas or fibroids are benign monoclonal tumours arising from the smooth muscle cells of the myometrium. Intracavitary abnormalities (polyps and fibroids) are the leading cause of AUB. They are present in 40% of the women who are referred by the general practitioner for abnormal uterine bleeding [1-3]. Fibroids are noted in histological reports in up to 80% of surgically excised uteri [4, 5]. Although the majority of fibroids are asymptomatic, up to 25% cause problems [6]. Fibroids can present with a variety of symptoms such as abnormal uterine bleeding, pelvic pain and they may impair fertility. Fibroids can have a negative impact on women's lives [7, 8], cause a major public health-care burden [9-11] and are worldwide still the leading cause for hysterectomy [12-15].

Imaging of the uterus (with ultrasound)

Diagnosis of uterine disorders is based upon patient medical history, physical (pelvic) examination and imaging. In gynaecology, (transvaginal) ultrasound is the most widely used modality due to its availability and cost-effectiveness. Together with patient's medical history and physical examination it provides a complete evaluation of the problem. Ultrasound for medical purpose was first reported in the late 1940's and further developed in the 1950s and 1960s [16]. Using sound waves different tissues can be transformed into a digital image without the use of X-radiation. Magnetic resonance imaging (MRI) is also an alternative to visualize the pelvic organs without radiation but a less available, more time consuming and more expensive option. Ultrasound is easy to re-locate and can be used in all settings (operating room, outpatient clinic etc.). It is of great importance in differentiating between benign and malignant pathology. For example, ultrasound is used in post-menopausal bleeding to differentiate between a benign diagnosis or (the possibility of) endometrial carcinoma. This lowers the need for more burdensome diagnostic methods [17-19]. Ultrasound can also differentiate between several benign disorders like fibroids and adenomyosis [20]. In the last two to three decades several minimal invasive therapies (drug and surgical) for different abnormalities have been developed and the number of hysterectomies decreased. The availability of these techniques require a more precise diagnosis of the uterine disorder. Depending on diagnosis, treatment options vary and therefore it is crucial to correctly diagnose and

classify any present pathology. Ultrasound (quality) has improved substantially over the past years and several techniques are added/combined to ultrasound to enhance visualisation and improve diagnosis. For example in three-dimensional (3D) ultrasound a volume (organ of interest) can be stored and analysed directly on the machine or offline at a personal computer whenever needed. Before implementing new techniques it is necessary to study diagnostic performance and accuracy.

Part I: imaging of the cavity

Visibility of the uterine cavity can be improved by infusion of saline or gel (picture). The diagnostic accuracy of two dimensional saline infusion sonography (2D SIS) for the detection of intrauterine abnormalities equals the diagnostic accuracy of hysteroscopy with a sensitivity of 95% and a specificity of 88% [21] with lower discomfort in comparison to a hysteroscopy [22].

Picture of an intracavitary abnormality visible with saline infusion sonography

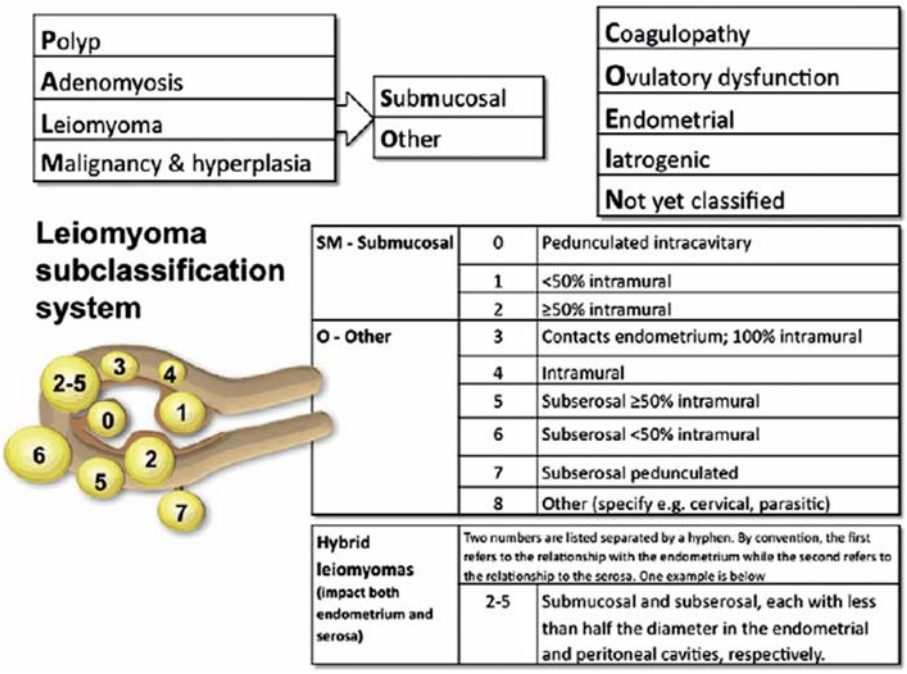
Still, 5% is missed at ultrasound and 12% is falsely diagnosed. Three-dimensional sonohysterography potentially enhances visualisation of the uterine cavity. It allows the examination of the uterus from any angle and in any plane including the coronal plane, which allows the examiner to more accurately measure size and the extent of protrusion of submucous fibroids into the uterine cavity [23-25]. Size (volume) and extent of protrusion are important determinants for the planning of hysteroscopic procedures in

terms of applied anaesthetics, used instruments and required level of experience of the surgeon [26-28]. Thus, an accurate diagnosis at SIS influences treatment strategy and may prevent unnecessary hysteroscopies. Reproducibility of 3D SIS is scarcely investigated and studies evaluating the accuracy of 3D SIS were mostly performed by experts, its accuracy in general clinical practice is unknown but possibly less accurate. When 2D SIS is inconclusive, 3D SIS might be of additional value, this needs to be studied too.

Part II: Imaging of uterine fibroids

In women with fibroids, one may find an enlarged uterus during physical examination [29]. Suspicion of fibroids at patients history and physical examination can be confirmed with imaging techniques (MRI, ultrasound). Diagnosing fibroids is not difficult using ultrasound (for an experienced sonographer) but can be challenging at times since pathology can appear similar to other diagnosis like adenomyosis, sarcomas, intracavitary polyps or haematoma. Since treatment strategies differ, additional techniques like 3D ultrasound, Doppler and elastography can be helpful to distinguish between these different disorders [30]. Fibroids are classified according to their location in the uterus using the FIGO classification of fibroids as shown in the figure below [31].

M.G. Munro et al. / International Journal of Gynecology and Obstetrics 113 (2011) 3–13



SM - Submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O - Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g. cervical, parasitic)
Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

A subserosal fibroid will be differently treated than a submucous fibroid. Submucosal fibroids (type 0-2) can be difficult to correctly classify on regular 2D ultrasound and general accuracy is low. Besides SIS, 3D ultrasound can help to diagnose correctly using the additional coronal plane which provides the ability to analyse the fibroid in relation to the endometrium in any desired plane. The accuracy of 3D ultrasound to detect congenital abnormalities of the uterus is very good but the accuracy to classify submucous fibroids is not widely studied. This could be potentially beneficial since it is easier for the patient and physician to perform a 3D ultrasound than SIS. Besides location, ultrasound provides additional information about number, size (diameter and volume) and vascularity of fibroids. Information about size and location are necessary for (surgical) treatment planning and for follow up in expectative management. With the increasing options for treatment, more women prefer minimal invasive treatment that preserves the uterus over radical surgery like hysterectomy. Vascularity plays a role in the choice of type of (minimal invasive) treatment. Tissues and tumours have their own vascular patterns. The vascularity of vital fibroids has a characteristic pattern: within the fibroids a low vessel count, while around the fibroid vessels are abundantly present [32]. MRI-based vascularity of the fibroids is correlated with the success rate of the uterine artery embolization (UAE) [33], while fibroid ablation is reported to be less suitable for fibroids with high vascularity [34, 35]. Thus, vascularity can be used to predict response to treatment. Assessing vascularity with MRI is an expensive and time-consuming procedure and alternatives such as Doppler ultrasound are available. Colour Doppler ultrasound (two dimensional) can provide information about vascularity, it is used to evaluate flow and resistance in blood vessels for example to diagnose carotid disease or placenta insufficiency. It can also help in the diagnosis of intracavitary polyps in visualising the pedicle artery [36]. Power Doppler ultrasound (three dimensional) can quantify vessels within a volume (for example an entire organ or tumour) expressed in vascular parameters. Power Doppler is reported to help differentiate between fibroids and adenomyosis [37] which are sometimes difficult to differentiate at conventional ultrasound. Power Doppler's vascular parameters are: Vascular Index (VI) representing the proportion of blood vessels within the tissue, Flow Index (FI) indicating the average flow velocity and Vascular Flow Index (VFI) as their product. How these parameters can be obtained in fibroids is not yet known and the reproducibility of 3D Power Doppler in fibroids has not yet been studied. Angiogenesis and vascularization are considered as crucial factors in fibroid development and growth [38, 39]. Besides predicting response to therapy it would be useful to predict fibroid behaviour. Currently there are no strong predictors for fibroid growth that can be used in daily practice. Fibroid growth over time is studied and showed to be very heterogeneous between and even within patients. Vascularity is never followed over time in fibroids and the relation of vascularisation and

growth neither. Determining growth potential of a distinct fibroid would be beneficial in clinical decision making. Potential fibroid growth is particularly relevant in patients with limited symptoms and for patients considering a (future) pregnancy.

Aims of this thesis:

This thesis will focus on validating several additional ultrasound techniques (3D SIS and 3D PD) and evaluate their accuracy in clinical setting aiming to improve diagnosis and subsequently improve (choice of) treatment of fibroids and polyps. We aim to answer the following questions;

PART I: Imaging of the uterine cavity

- Is three dimensional gel instillation sonography (3D GIS) a reproducible method in detecting intracavitary lesions of the uterus and can it differentiate between type of abnormality?
- What is the accuracy of 3D GIS for detecting intracavitary lesions of the uterus in clinical practice?
- Is 3D GIS more accurate than 2D GIS? Are they more accurate if combined in the detection of intracavitary polyps and submucous fibroids?
- Will a higher accuracy (more correct diagnose) improve planning/choice of treatment concerning polyps and submucosal fibroids?
- What is reported in the literature about accuracy of 3D SIS/GIS (compared to 2D SIS/GIS) in the detection of focally growing acquired lesions?
- What is the accuracy and reliability of 3D ultrasound in classifying submucous fibroids?

PART II: Imaging of uterine fibroids

- How do we obtain and calculate 3D PD volumes and vascular parameters (VI, FI and VFI) in uterine fibroids?
- Which vascular parameter has the best discriminating ability?
- What is the reproducibility of 3D PD US in fibroids?
- Are vascular parameters in fibroids dependent on machine settings? What ultrasound settings are of influence in fibroids?
- Can we predict fibroids growth measuring vascular parameters in fibroids? We hypothesise that well vascularised fibroids grow faster than poorly vascularised ones.
- Can vascularity predict symptoms (fibroid specific and quality of life)?

Outline of this thesis

PART I: Imaging of the cavity

- **Chapter II** determines the interobserver and intraobserver variability of 3D GIS in the assessment of intrauterine abnormalities using stored 3D GIS volumes.
- **Chapter III** will address the question whether we can improve diagnoses and preoperative planning (and subsequently treatment) with 3D GIS. In a prospective observational cohort study, the diagnostic value of 3D GIS in addition to 2D GIS in the assessment of intrauterine abnormalities will be studied.
- **Chapter IV** gives an overview of the literature in a systematic Cochrane review and meta-analysis reporting accuracy of 3D SIS (compared to 2D SIS).
- **Chapter V** studies the role of three-dimensional sonography (without saline or gel installation) in the assessment of submucous fibroids.

PART II: Imaging of uterine fibroids

- In **Chapter VI** we evaluate the interobserver agreement and discriminating value of three-dimensional Power Doppler ultrasound (3D PDUS) in patients with fibroids.
- **Chapter VII** studies the influence of the cardiac cycle and different gain settings on 3D PD vascular parameters in the assessment of fibroid vascularisation. Secondly, several off line methods for fibroid volume and fibroid capsule volume calculation, and VI calculation in fibroids will be studied.
- The aim of **Chapter VIII** is to analyse fibroid growth in relation to fibroid vascularisation using 3D PD ultrasound. A prospective observational cohort study was conducted to follow women with fibroids during one year.
- **Chapter IX** will address to the question if symptoms observed with questionnaires (PBAC, UFS-QOL) are related to vascularity of fibroids.
- In **Chapter X** we discuss the results of our studies and their clinical implications and future research suggestions.
- **Chapter XI** will summarise all results in English and Dutch.

REFERENCES

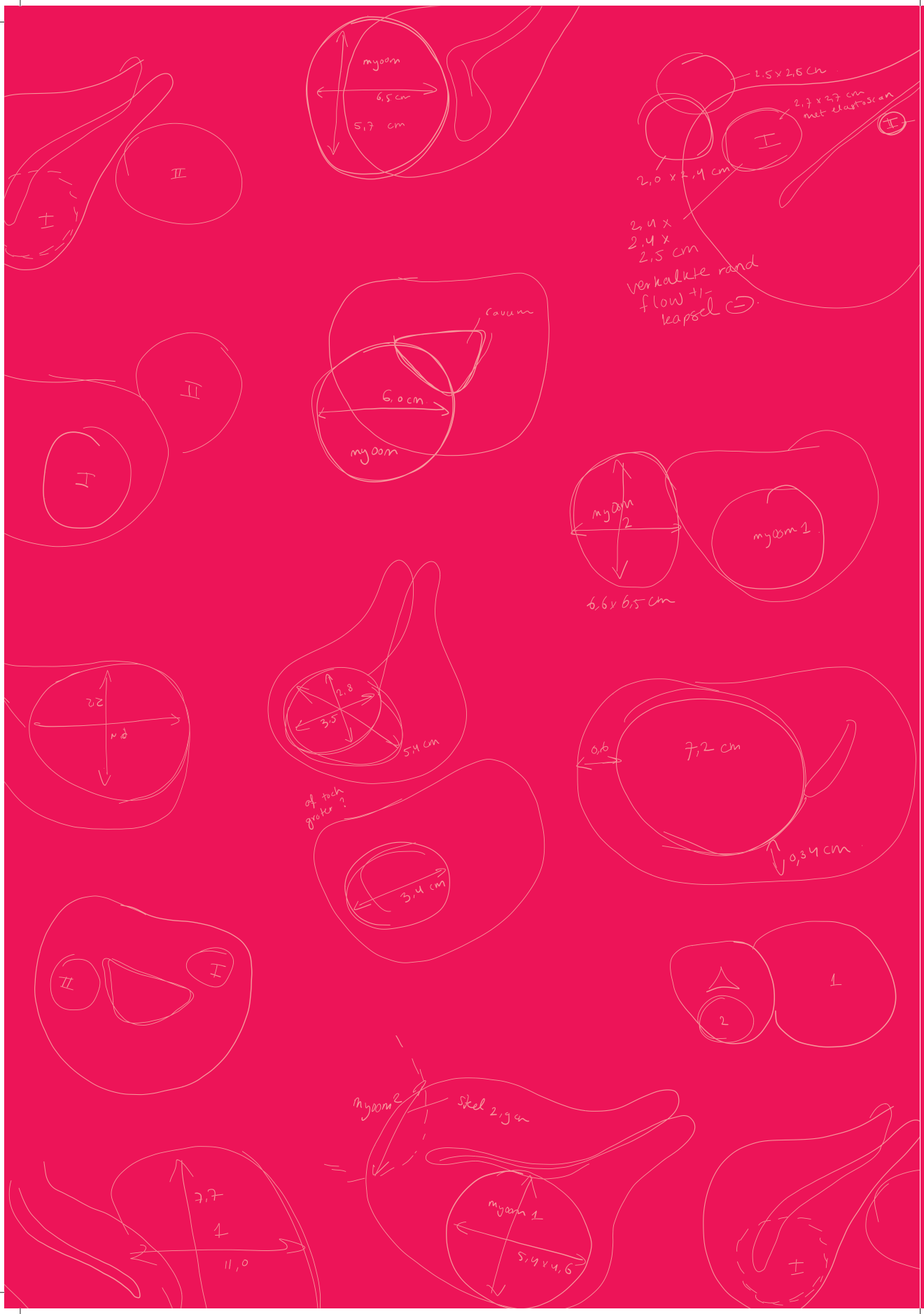
1. Emanuel MH, Verdel MJ, Wamsteker K, Lammes FB. A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding: clinical implications. Am J Obstet Gynecol. 1995 2/1995;172(2 Pt 1):547-52.
2. Tur-Kaspa I, Gal M, Hartman M, Hartman J, Hartman A. A prospective evaluation of uterine abnormalities by saline infusion sonohysterography in 1,009 women with infertility or abnormal uterine bleeding. Fertil Steril. 2006 Dec;86(6):1731-5.
3. Van den Bosch T, Ameye L, Van Schoubroeck D, Bourne T, Timmerman D. Intra-cavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. Facts Views Vis Obgyn. 2015;7(1):17-24.
4. Buttram VC, Jr., Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981 1981;36(4):433-45.
5. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol. 1990 1990;94(4):435-8.
6. Stewart EA. Uterine fibroids. Lancet. 2001 1/27/2001;357(9252):293-8.
7. Spies JB, Coyne K, Guaou GN, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002 2/2002;99(2):290-300.
8. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol. 2013 Oct;209(4):319 e1- e20.
9. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012 Mar;206(3):211 e1-9.
10. Downes E, Sikirica V, Gilabert-Estelles J, Bolge SC, Dodd SL, Maroulis C, et al. The burden of uterine fibroids in five European countries. Eur J Obstet Gynecol Reprod Biol. 2010 9/2010;152(1):96-102.
11. Fernandez H, Farrugia M, Jones SE, Mauskopf JA, Oppelt P, Subramanian D. Rate, type, and cost of invasive interventions for uterine myomas in Germany, France, and England. J Minim Invasive Gynecol. 2009 1/2009;16(1):40-6.
12. Renwick M. Variations in surgery rates: implications for quality. Aust Clin Rev. 1991 1991;11(4):159-63.
13. Pokras R, Hufnagel VG. Hysterectomy in the United States, 1965-84. Am J Public Health. 1988 7/1988;78(7):852-3.
14. Luoto R, Kaprio J, Keskimaki I, Pohjanlahti JP, Rutanen EM. Incidence, causes and surgical methods for hysterectomy in Finland, 1987-1989. Int J Epidemiol. 1994 4/1994;23(2):348-58.
15. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990-1997. Obstet Gynecol. 2002 2002;99(2):229-34.

16. Campbell S. A short history of sonography in obstetrics and gynaecology. Facts Views Vis Obgyn. 2013;5(3):213-29.
17. Dr. W.J.K. Hehenkamp g, NVOG (voorzitter). . Heavy menstrual bleeding [Hevig menstrueel bloedverlies]. . Guideline NVOG 2013;1-196 2013.
18. (NICE). NIfHaCE. Heavy menstrual bleeding: assessment and management. NICE clinical guideline 44 2007, last updated: August 2016.
19. Gynecology AOa. Guideline ACOG technology assessment no. 8: Sonohysterography. 2012.
20. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015 Sep;46(3):284-98.
21. de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG. 2003 10/2003;110(10):938-47.
22. van Dongen H, de Kroon CD, van den Tillaart SA, Louwe LA, Trimbos-Kemper GC, Jansen FW. A randomised comparison of vaginoscopic office hysteroscopy and saline infusion sonography: a patient compliance study. BJOG. 2008 Sep;115(10):1232-7.
23. Lee C, Salim R, Ofili-Yebovi D, Yazbek J, Davies A, Jurkovic D. Reproducibility of the measurement of submucous fibroid protrusion into the uterine cavity using three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol. 2006 11/2006;28(6):837-41.
24. Mavrelos D, Naftalin J, Hoo W, Ben-Nagi J, Holland T, Jurkovic D. Preoperative assessment of submucous fibroids by three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol. 2011 9/2011;38(3):350-4.
25. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol. 1993 11/1993;82(5):736-40.
26. Betjes HE, Hanstede MM, Emanuel MH, Stewart EA. Hysteroscopic myomectomy and case volume hysteroscopic myomectomy performed by high- and low-volume surgeons. J Reprod Med. 2009 7/2009;54(7):425-8.
27. Hanstede MF, Stewart EA. Do high -volume surgeons have better outcome for abdominal myomectomies? 2006 2006.
28. Emanuel MH. 3D echoscopie van het cavum uteri. Reproductieve geneeskunde, gynaecologie en obstetrie, anno 2009; 2009. p. 392-5.
29. Stoelinga B, Huirne J, Heymans MW, Reekers JA, Ankum WM, Hehenkamp WJ. The estimated volume of the fibroid uterus: a comparison of ultrasound and bimanual examination versus volume at MRI or hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2015 Jan;184:89-96.
30. Stoelinga B, Hehenkamp WJ, Brolmann HA, Huirne JA. Real-time elastography for assessment of uterine disorders. Ultrasound Obstet Gynecol. 2014 Feb;43(2):218-26.

31. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011 Apr;113(1):3-13.
32. Andrea Tinelli AM. Uterine Myoma, Myomectomy and Minimally Invasive Treatments. 2014;Chapter 8-imaging of myomas(ISBN 9783319103051):109-28.
33. Isonishi S, Coleman RL, Hirama M. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. AJOG. 2008 2008;198(3):270-e1.
34. Funaki F, Fukunishi H, Funaki T, Sawada K, Kaji Y, Maruo T. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. AJOG. 2007 2007;196(2):e1-e6.
35. Yoon SW, Lee C, Kim KA, Kim SH. Contrast-Enhanced Dynamic MR Imaging of Uterine Fibroids as a Potential Predictor of Patient Eligibility for MR Guided Focused Ultrasound (MRgFUS) Treatment for Symptomatic Uterine Fibroids. Obstet Gynecol Int. 2010 2010;2010.
36. Timmerman D, Verguts J, Konstantinovic ML, Moerman P, Van Schoubroeck D, Deprest J, et al. The pedicle artery sign based on sonography with color Doppler imaging can replace second-stage tests in women with abnormal vaginal bleeding. Ultrasound Obstet Gynecol. 2003 Aug;22(2):166-71.
37. Sharma K, Bora MK, Venkatesh BP, Barman P, Roy SK, Jayagurunathan U, et al. Role of 3D Ultrasound and Doppler in Differentiating Clinically Suspected Cases of Leiomyoma and Adenomyosis of Uterus. J Clin Diagn Res. 2015 Apr;9(4):QC08-12.
38. Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update. 2014 Mar-Apr;20(2):194-216.
39. Fleischer R, Weston GC, Vollenhoven BJ, Rogers PA. Pathophysiology of fibroid disease: angiogenesis and regulation of smooth muscle proliferation. Best Pract Res Clin Obstet Gynaecol. 2008 8/2008;22(4):603-14.

PART I

Imaging of the cavity


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

02

Reproducibility of three-dimensional gel installation sonohysterography in the assessment and classification of intrauterine abnormalities

Lotte L. Nieuwenhuis
Marjolein (A.J.) Bij de Vaate
Wouter J.K. Hehenkamp
Martijn W. Heymans
Marchien (W.M.) van Baal
Hans A.M. Brölmann
Judith A.F. Huirne

Eur J Obstet Gynecol Reprod Biol. 2014 Aug;179:141-6

ABSTRACT

Objective: Purpose of this study is to determine the interobserver and intraobserver variability of 3D GIS in the assessment of intrauterine abnormalities.

Study design: forty five 3D volumes were randomly selected from a larger prospective cohort study that studied the diagnostic accuracy of 3D GIS in addition to 2D GIS. To study interobserver agreement volumes were reviewed by two independent examiners. One examiner reviewed these samples twice with an interval of 1 month in a random order. Interobserver and intraobserver agreement was tested with Cohen's Kappa coefficient and shown in Bland and Altman plots. Quality of the 3D volumes was evaluated.

Results: Cohen's Kappa for interobserver variability for type of abnormalities (none, polyp, fibroid, other) was 0.64 and for presence of a fibroid (fibroid yes/no) 0.77. Agreement on type of fibroid was 0.59. Intraobserver agreement was almost perfect for type of abnormality (Cohen's kappa of 1.0) and good for fibroid diameter. Quality of the 3D volumes was poor in 11 out of 45 cases. Reproducibility increased when poor quality images were excluded.

Conclusion: Substantial to perfect interobserver and intraobserver agreement for 3D GIS in the diagnoses of intrauterine abnormalities was found. 3D GIS interobserver and intraobserver agreement are good for fibroid diameter and moderate for volume and protrusion.

Key words: saline or gel infusion, sonohysterography, three dimensional, reproducibility, intrauterine abnormalities

INTRODUCTION

Intracavitary pathology (polyps, submucous fibroids) is expected in more than 40% of the women who are referred by the general practitioner for abnormal uterine bleeding [1]. Other associated symptoms are dysmenorrhoea, infertility or miscarriage [2;3]. Sonohysterography is a procedure in which fluid (saline or gel) is instilled transcervically into the uterine cavity to provide enhanced visualisation of the endometrial lining during transvaginal ultrasound examination. Both saline infusion sonohysterography (SIS) and GIS are simple, safe, well tolerated and accurate techniques in the assessment of intra-uterine abnormalities[4;5]. Three-dimensional SIS enhances visualisation of the uterine cavity and is highly accurate in the diagnosis of uterine abnormalities[6] and can provide an alternative to hysteroscopy in the diagnostic workup of abnormal uterine bleeding instead of hysteroscopy [7]. The advantage of 3D SIS (over 2D SIS) lies in the fact that it provides very accurate information about diameter and extent of sub mucous protrusion of fibroids into the uterine cavity [8-10]. Mavrelos [9] reported that in particular these parameters (diameter and protrusion) are of significant influence on completeness of resection. The latter suggests that 3D provides useful information for the clinical practice.

Although much has been written on the accuracy of 3D SIS, little is known about its reproducibility. Without good reproducibility, even a highly accurate test cannot be of use in general practice. Dueholm et al [11] reported intermediate agreement for the interobserver agreement on conventional transvaginal sonography for detecting/ excluding uterine cavity abnormalities. To our best knowledge, only three studies [6;8;12] reported about 3D SIS reproducibility and none on the reproducibility of 3D GIS. Our objective is to evaluate the interobserver and intraobserver agreement of 3D gel installation sonohysterography (GIS) in the diagnosis for intracavitary abnormalities, its classification and diameter, volume and percentage of protrusion into the uterine cavity of submucous fibroids. Main outcome is identification of an abnormality and type of abnormality.

MATERIALS AND METHOD

Data collection, storage and sample selection

We used stored 3D volume datasets generated from a larger prospective cohort study assessing the diagnostic accuracy of 3D GIS in addition to 2D GIS[13]. Women with abnormal uterine bleeding, dysmenorrhoea, recurrent miscarriage, infertility or suspicion of an intrauterine abnormality on regular ultrasound received a 2D GIS (n=855). 3D GIS

volumes (n=203) were obtained when an intracavitary abnormality was suspected at 2D GIS. A random sample of 45 3D volumes was taken by an independent statistician unfamiliar with the content of the volumes, patients, sonographic or hysteroscopic results. 3D volumes were reviewed independently by two examiners between January and March 2012 (MvdV, LLN).

Generation of 3D volumes

A 3D volume was generated by an automatic sweep of the mechanical transducer (trans vaginal transducer 5-8 MHz), with the ultrasound probe in the midsagittal plane and the uterus within the scan sector. The sweeps were taken by experienced and sufficiently trained sonographers in a daily practice in the VU medical centre, Amsterdam, the Netherlands. The volumes were stored digitally (mvl file) on a personal computer. SonoView Pro- 1.5 VOCAL software and 3D XI viewer (Samsung Medison) were used for analysing 3D volumes.

Evaluation of the stored 3D volumes

For interobserver agreement 3D volumes were reviewed by two independent examiners (residents), familiar (after training) with the interpretation of 3D ultrasound. Both were blinded for the 2D GIS and hysteroscopy findings. For intraobserver agreement, 25 of these volumes were randomly reviewed twice by the same observer. A minimum of one month between the two measurements was set. Volumes were reviewed in a different random order. Both observers were blinded for patient characteristics, symptoms, 2D GIS, hysteroscopic or histological outcomes.

Image quality evaluation

Each image was scored for its quality of visualisation and possibility to analyse. Quality was scored on a lickert scale from 1-5, 1 representing very poor quality and 5 representing almost perfect image quality. Quality depended on contrast, sharpness and brightness of the image, air bubbles and other artefacts, distension and total visualisation in case of an intrauterine abnormality. Each category (contrast, sharpness, etc) was weighted and could render a point.

Cavity evaluation

A normal cavity was defined as an undistorted outline of the endometrium. The following details of the intrauterine abnormalities were recorded: origin, diameter and protrusion into the uterine cavity. Smooth margined echogenic masses with a homogenous texture were described as polyps, while structures of mixed echogenicity disrupting the endometrial continuity were described as submucous fibroids [14]. This

resulted in 4 categories of abnormality: 'none', 'fibroid', 'polyp' or 'other', the latter consisting of abnormalities that could not be categorised as previously mentioned. Presumed intrauterine fibroids were classified into subtypes (type 0, 1, 2) according to the degree of protrusion into the uterine cavity (type 0 100% intracavitary, type 1 >50% protrusion into the cavity, type 2 <50% protrusion into the cavity)[10].

Evaluation of fibroid protrusion

A standardised method was used for the measurement of fibroid protrusion as previously reported by Lee et al [8] (see figure 1). Measurement started with the multiplanar display (software: XI viewer, Samsung-Medison, Hoofddorp, the Netherlands). Fibroids located anteriorly, posteriorly or fundally were analysed in the longitudinal or sagittal plane. Lateral fibroids were analysed in the coronal or transversal plane. First the fibroid was localised, by taking the frame with the largest diameter. Then the z-axis was rotated until the y-axis was perpendicular to the fibroid. When in good position, the y-axis was rotated. While rotating the y-axis, the fibroid protrusion ratio (part intracavitary and part myometral) should not change. When the ratio was not changing, a line was drawn were the fibroid entered the endometrial-myometrial junction. A section of the fibroid protruding into the cavity (A) and a part confined to the myometrium (B) were both measured. Protrusion into the cavity was calculated using (A/ (A+B) x 100).

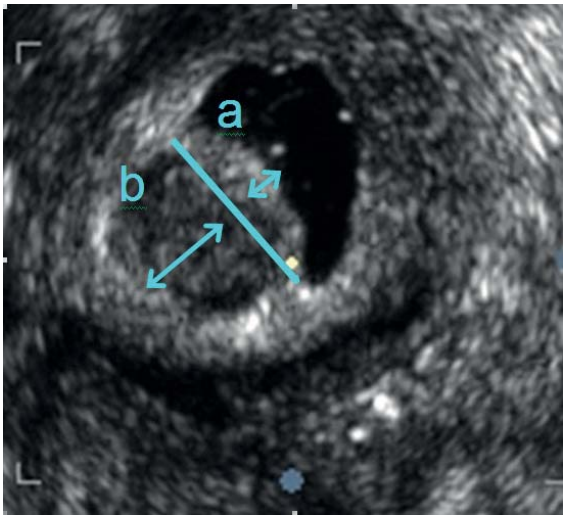


Figure 1. Measuring protrusion in a submucous fibroid in coronal plane (picture taken during gel installation sonohysterography). A. protrusion into the cavity, B. part of the fibroid in the myometrium. Fibroid protrusion into the cavity is calculated using (A/ (A+B) x100).

Evaluation of fibroid volume

Volumes of the fibroids were calculated using XI VOCAL manual contour mode (software: XI viewer) according to a standardized protocol. The main contour axis was positioned in the centre of the fibroid. In the reference plane, both poles were set at the boundaries of the fibroid. The manual contour mode was applied to outline the shape of the whole fibroid in 5 different sections. The contour was redefined if necessary. A volume was then automatically calculated. We also calculated fibroid volumes using the formula $1/6*pi*d^3$ and plotted them with the measured ones using VOCAL to show agreement.

Statistical analysis

Overall interobserver agreement (reproducibility) and intraobserver agreement (repeatability) was tested for image quality, presence of intrauterine abnormalities, type of abnormality (none, fibroid, polyp, other) and type of fibroid (0, I, II). Percentage agreement between observers was determined. The interobserver and intraobserver agreement of categorical data (nature and type of abnormality) was tested with Cohen's Kappa coefficient. The weighted version was used in case of ordinal data.

Kappa was defined as the difference between observed and expected agreement (by chance), expressed as a fraction of the maximum possible difference. A kappa value of <0.20 indicates slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement [15].

We used the Bland and Altman plot to show agreement (for continuous data) between measurements of two observers and agreement between two measurements for fibroid diameter, volume and protrusion [16;17]. In this graphical method the differences between the two measurements are plotted against the averages of the two measurements. Horizontal lines are drawn at the mean difference, and at the 95% limits of agreement (LOA), which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. The data were log transformed in case there was a relationship between the mean and magnitude of the difference. Mean antilog was calculated to help interpret differences between measurements.

For sensitivity analysis we explored if results for good and poor quality volumes would differ. Interobserver agreement for all categories as mentioned above was also calculated for only good quality volumes.

All statistical analyses were performed with SPSS 20 and R software.

RESULTS

Three dimensional volumes were reviewed independently by two examiners. Baseline characteristics of patients and measurements are listed in *table 1*.

Image quality was poor in 11 out of 45 cases. Poor image quality was mostly caused by lack of distension (8 out of 11 volumes), followed by poor sharpness and brightness of the image (4 times), incomplete visualisation of the uterus (4 times) and air bubbles (3 times). A combination of factors was frequently the cause of poor quality (for example suboptimal distension in combination with poor sharpness or air bubbles).

Table 1. Baseline characteristics for patients and measurements using 3-dimensional gel installation sonohysterography

FEATURE	
Patient age (years)	43.0 (SD 8.76)
Nulliparity	49%
Indication for GIS	N = 45 (100%)
Bleeding problems	30 (67%)
Fertility problems	10 (22%)
Other	5 (11%)
Histology	N = 45 (100%)
Polyp	15 (33%)
Fibroid	25 (56%)
Other†	5 (11%)
Total of evaluated 3D GIS volumes	N = 45 (100%)
Number of good quality volumes*	34 (76%)
Number of polyps	17
Number of fibroids	22
Fibroid	Median (IQR-range**)
Diameter (cm)	1.9 (1.7-3.0)
Volume (cm3)	1.9 (0.7-7.8)
Fibroid protrusion (%)	33.0 (22-62)

* Each image was scored for its quality of visualisation and possibility to analyse. ** IQR range = interquartile range (between the 25 and 75 percentile). † Other was defined as placental rest, endometrial thickening or atrophy)

Table 2. Cohen's Kappa Coefficient for INTER and INTRA observer agreement for 3-dimensional gel installation sonohysterography

PARAMETER	3D GIS INTER OBSERVER Between 2 observers (all images)		3D GIS INTER OBSERVER Only good quality images used		3D GIS INTRA OBSERVER 2 measurements of 1 observer	
	% agreement (n/n†)	Cohen's Kappa (95% CI)	% agreement (n/n†)	Cohen's Kappa (95% CI)	% agreement (n/n†)	Cohen's Kappa (95% CI)
Image Quality (poor/good)	84 (38/45)	0.60 (0.36-0.85)	n.a.	n.a.	92 (23/25)	0.0
Abnormality (yes/no)	93 (37/40*)	-0.034 (**)	88 (30/34)	-0.046	100 (25/25)	1.0
Type of abnormality (*none, polyp, fibroid, other)*	71 (32/45)	0.53 (0.35-0.71)	79 (27/34)	0.64 (0.44-0.85)	100 (25/25¶)	1.0
Polyp (yes/no)*	76 (34/45)	0.56 (0.35-0.77)	85 (29/34)	0.71 (0.48-0.94)	92 (23/25)	0.84 (0.63-1.0)
Fibroid (yes/no)*	80 (36/45)	0.63 (0.44-0.82)	88 (30/34)	0.77 (0.57-0.97)	100 (25/25)	1.0
Type of fibroid (0,I, II)*	81 (13/16§)	0.59 (0.24-0.94)	77 (10/13)	0.56 (0.20-0.92)	67 (10/15)	0.50 (0.18-0.82)

† n/n = number of agreed cases/ total number of cases. * 5 out of 45 were reviewed as unknown and calculated as missing. § Total number of fibroids =22. In 6 cases there was no agreement on type of abnormality. ** Standard Error (SE) (to calculate 95% Confidence Interval) was not provided by SPSS due to negative Kappa value

Table 3. INTER and INTRA observer agreement for various fibroid measurements using 3-dimensional gel installation sonohysterography

FIBROID PARAMETER	INTER OBSERVER (BETWEEN TWO OBSERVERS)					INTRA OBSERVER (TWO MEASUREMENTS FROM ONE OBSERVER)				
	N†	Mean diff Log	95% LOA Log	Mean diff Anti log	95% LOA Anti log	N†	Mean diff Log	95% LOA Log	Mean diff Anti log	95% LOA Anti log
Diameter	17	-0.02	-0.34 - 0.31	0.98	0.71 - 1.36	15	-0.04	-0.42 – 0.34	0.96	0.65 – 1.41
Protrusion	12	0.19	-1.25 – 1.63	1.21	0.29 - 5.10	13	-0.10	-1.34 – 1.14	0.90	0.26 – 3.13
Volume	10	0.55	-0.58 – 1.69	1.74	0.56 – 5.42	10	0.12	-1.08 – 1.13	1.13	0.34 – 3.78

† N= number of measurements. Numbers are different for the several parameters because in some cases one of the observers could not perform the measurement (due do disagreement in type of abnormality or poor image quality). * 95% LOA: 95% limits of agreement. LOA were calculated for log transformed and anti log data.

Interobserver

Cohen's Kappa for interobserver agreement is listed in *table 2*. For almost all parameters agreement improved when poor quality (n= 11) volumes were excluded (*table 2*); for example type of abnormality (none, polyp, fibroid, other) improved from 0.56 to 0.64.

Visual inspection of the Bland and Altman plots (figure 2a-c) between 2 observers showed good agreement for fibroid diameter. Antilog of mean difference for diameter between the two observers was 0.98 (95% limits 0.71-1.36); diameter was measured 2% (or 1.02 times) larger by observer 2 compared to observer 1 (table 3). For fibroid diameter the vast majority of measurements lie between the 20% limits of agreement (-0.24 - 0.16). Measurements for protrusion show moderate agreement. For fibroid volume, there is a systematic mean difference of 1.74 (table 3). Agreement for fibroid volume between observers was moderate. Agreement between volumes calculated using VOCAL versus volumes calculated with the formula $1/6*pi*d^3$ was moderate to good (figure 3).

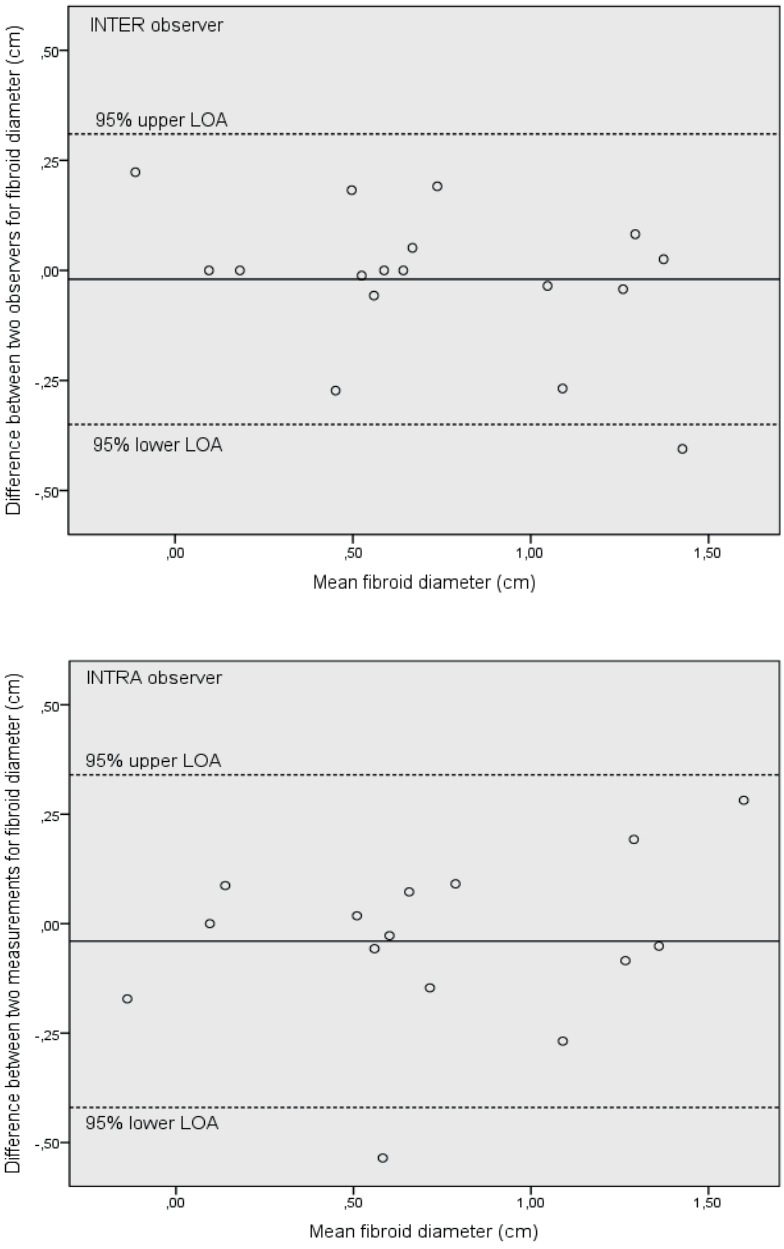


Figure 2a. Agreement between two observers (top) and between two measurements (bottom) for fibroid diameter using 3D GIS*. *3D GIS: three dimensional sonohysterography. Log transformed data were used for the plots.

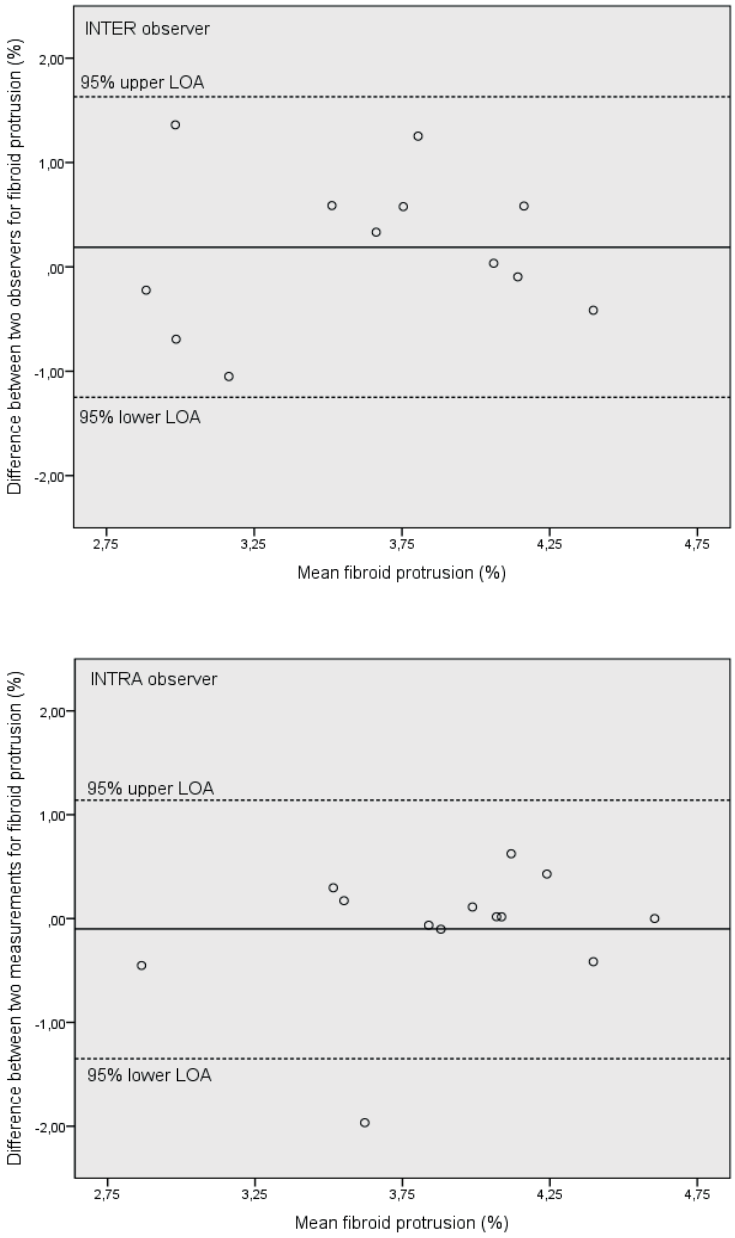


Figure 2b. Agreement between two observers (top) and between two measurements (bottom) for fibroid percentage protrusion using 3D GIS*. *3D GIS: three dimensional sonohysterography. Log transformed data were used for the plots.

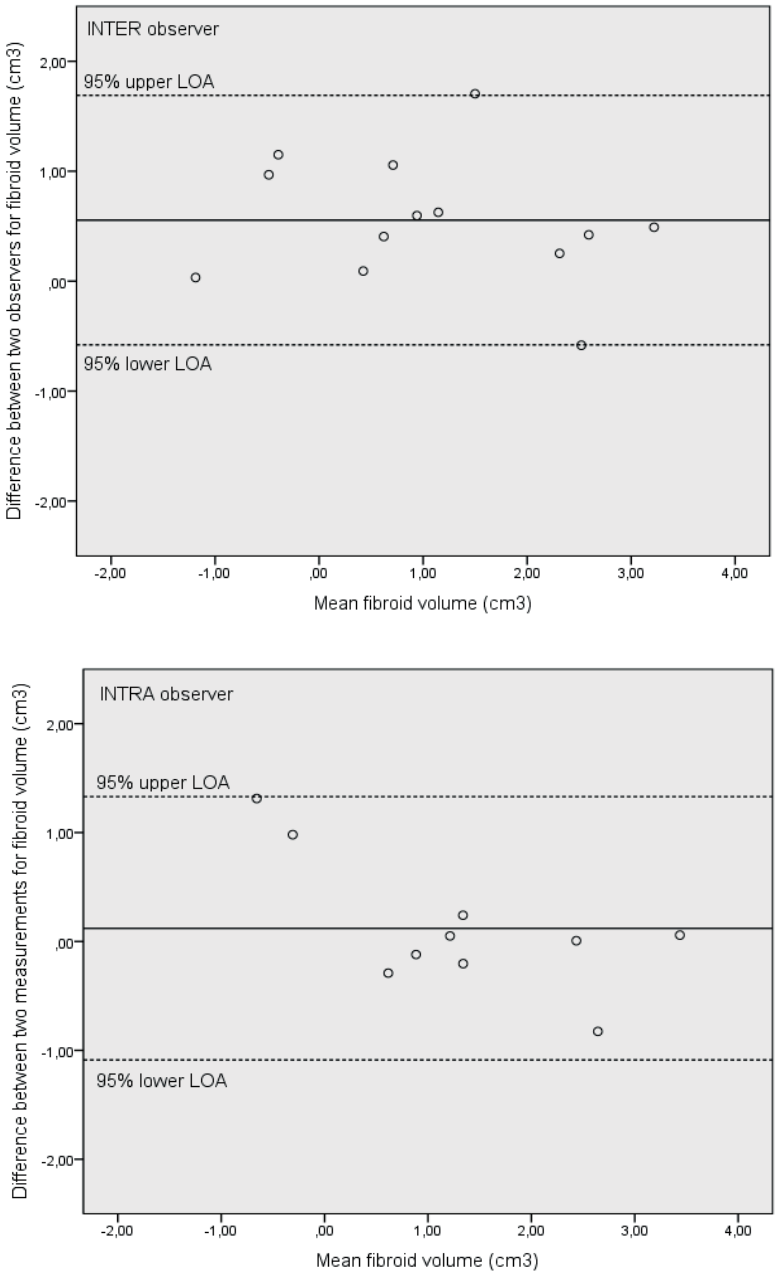


Figure 2c. Agreement between two observers (right) and between two measurements (left) for fibroid volume using 3D GIS*. *3D GIS: three dimensional sonohysterography. Log transformed data were used for the plots.

Intraobserver

Almost perfect agreement was found for presence and type of abnormality with Cohen's Kappa value of 1 (*see table 2*). Bland and Altman plots were made for agreement between two measurements by one observer (figure 2a-c). Intraobserver plots show good agreement for diameter and moderate to good agreement for protrusion and volume.

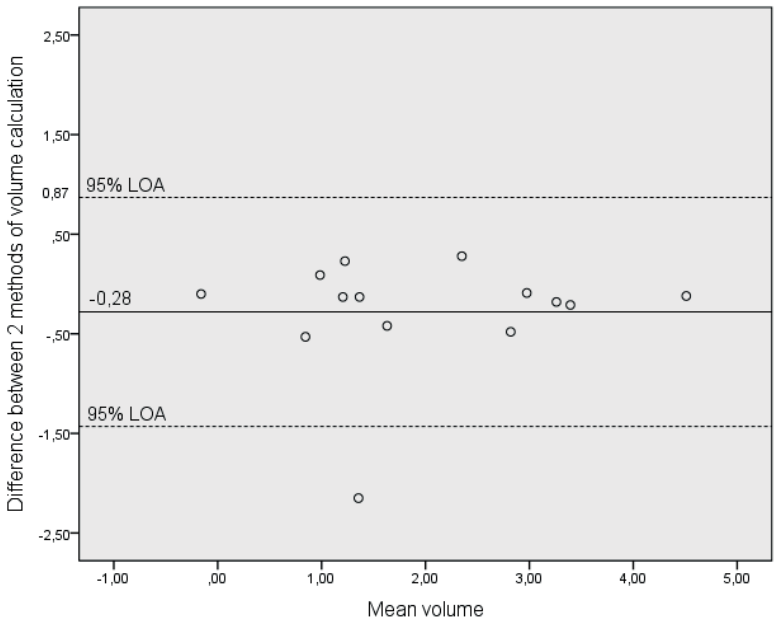


Figure 3. Agreement for two different methods* of fibroid volume calculation. *We calculated fibroid volumes using the formula 1/6*pi*d^3 (volume of a sphere) and we measured fibroid volumes using 3D VOCAL manual contour mode. Log transformed data were used.

COMMENT

Main findings

Interobserver and intraobserver agreement on type of abnormality and the presence of a fibroid or polyp was substantial. Agreement for both interobserver and intraobserver was lower but still moderate for type of fibroid. Moderate agreement was found for inter and intra-observer on fibroid protrusion and volume, good agreement was found for diameter..

Strengths and limitations of our study

One of our strengths is that we used a random sample of volumes independent of image quality or diagnosis from a larger cohort study where in a standardized manner 3D volumes were generated. We defined clear criteria how to estimate type, diameter, volume and percentage of fibroid protrusion into the cavity. A limitation of our study is that we included patients with a suspected intra-uterine abnormality, resulting in a limited number of patients without uterine abnormalities. To be expected since 3D GIS is usually planned when 2D sonography raises suspicion of an abnormality. Limited number of patients without uterine abnormalities resulted in sometimes poor or negative kappa values due to asymmetrical two by two tables. This influences the real agreement because kappa is a poor indicator in this situation. Kappa can have the tendency to take the observed categories' frequencies as given, which may underestimate the agreement for a category that is commonly used.

Interpretation of the results

Few studies report about 3D GIS interobserver agreement. Results from these studies are in some cases not directly comparable with ours because of differences in study population (only endometrial malignancy, only fibroids) and outcome parameters (not specified variables). Interobserver agreement on type of abnormality was substantial. Similar results were reported in two other studies [6;12]. De Kroon et al [6] reported substantial interobserver agreement in histological diagnosis. Though it is not clearly noted what definition was used for 'histologic diagnoses', the reported Kappa is similar to ours. The interobserver agreement for the presence of a focal laesion by Opolskiene et al[12] was also substantial.

For reproducibility in percentage of fibroid protrusion, Lee et al[8] reported a higher kappa value for classifying fibroids as greater or less than 50% confined to the myometrium. An explanation for the difference in results might be the quality of images. Our images resemble a general practice and show a relatively high percentage of poor quality

volumes. Quality may be affected because a 3D sweep was performed after 2D GIS. Gel could be leaking out of the cavity which might have let to less distension. An option is to perform 3D prior to 2D scanning to prevent this possible problem. Shadows from fibroids and insufficient penetration of the ultrasound are also a problem in the evaluation of fibroids. In the study of Lee et al[8], all 3D volumes were made by the same experienced observer. Differences in level of experience may also be of influence. Our observers are residents with moderate experience, though sufficiently trained for reviewing 3D GIS. Our agreement in the classification of intra-uterine abnormalities corresponds with the agreement found by Beemsterboer et al[4] for experienced observers in the assessment of uterine abnormalities using 2D GIS. However, we can not exclude that some learning curve in the measurement of protrusion may have played a role in the low agreement on fibroid type. Although measurements were standardized it still is complex to find the optimal plane for evaluation. Differences in taken plane may induce large differences in outcomes. The same applies to volume measurements. After reviewing the measurements, we may explain the systematic difference by the fact that a wider outline of the fibroid (including its capsule) was chosen by the first observer. Were to place the calipers may be effected by experience.

For fibroid diameter the agreement was good and moderate for volume. These results are in accordance to previously reported studies. Fibroid diameter is recognized to be an important preoperative predictor of complete resection [9;18-20]. Hart et al[20] reported that fibroids > 3cm were more likely to require two stage procedures and others [18;19;21] suggest that an expert should operate large fibroids (in order to reduce incomplete resection rates).

Clinical implications

Our results support the hypothesis that reproducibility of 3D GIS is substantial to good for most parameters. Based on the study results we may conclude that 3D GIS reproducibility, with respect to small sample size, is moderate to good even when used in general practice. Secondly, 3D GIS is reported to be very accurate[6;7;22]. We can prudently say that 3D GIS is a diagnostic technique with reproducible results and could make a trustworthy instrument that might be of value in clinical practise for diagnoses and preoperative prediction of complete resection. Future research should contain larger studies to reveal the real utility of 3D GIS.

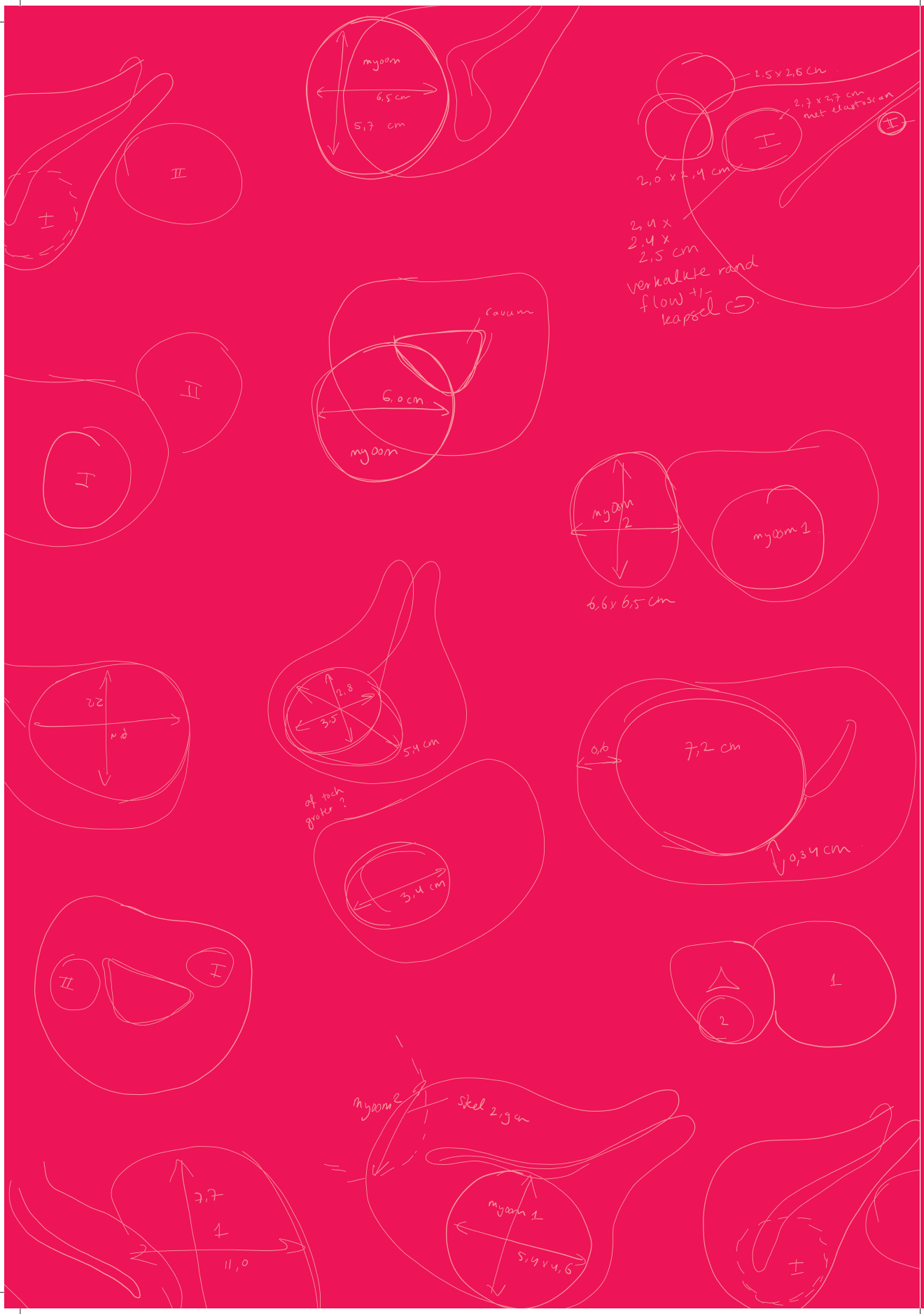
Conclusion

This study showed substantial interobserver agreement for 3D GIS in the diagnoses of intrauterine abnormalities. Intraobserver agreement is almost perfect for type of abnormality. 3D GIS inter and intraobserver is good for measuring fibroid diameter and moderate for volume and percentage protrusion.

REFERENCES

1. Emanuel MH, Verdel MJ, Wamsteker K, Lammes FB. A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding: clinical implications. Am J Obstet Gynecol 1995 Feb;172(2 Pt 1):547-52.
2. Acien P. Reproductive performance of women with uterine malformations. Hum Reprod 1993 Jan;8(1):122-6.
3. Raga F, Bauset C, Remohi J, Bonilla-Musoles F, Simon C, Pellicer A. Reproductive impact of congenital Mullerian anomalies. Hum Reprod 1997 Oct;12(10):2277-81.
4. Beemsterboer SN, Thurkow AL, Verstraeten R, Brolmann HA. Reproducibility of saline contrast sonohysterography for the detection of intracavitary abnormalities in women with abnormal uterine bleeding. Ultrasound Obstet Gynecol 2008 Apr;31(4):445-9.
5. Bij de Vaate AJ, Brolmann HA, van der Slikke JW, Emanuel MH, Huirne JA. Gel instillation sonohysterography (GIS) and saline contrast sonohysterography (SCSH): comparison of two diagnostic techniques. Ultrasound Obstet Gynecol 2010 Apr;35(4):486-9.
6. de Kroon CD, Louwe LA, Trimbos JB, Jansen FW. The clinical value of 3-dimensional saline infusion sonography in addition to 2-dimensional saline infusion sonography in women with abnormal uterine bleeding: work in progress. J Ultrasound Med 2004 Nov;23(11):1433-40.
7. Makris N, Skartados N, Kalmantis K, Mantzaris G, Papadimitriou A, Antsaklis A. Evaluation of abnormal uterine bleeding by transvaginal 3-D hysterosonography and diagnostic hysteroscopy. Eur J Gynaecol Oncol 2007;28(1):39-42.
8. Lee C, Salim R, Ofili-Yebovi D, Yazbek J, Davies A, Jurkovic D. Reproducibility of the measurement of submucous fibroid protrusion into the uterine cavity using three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol 2006 Nov;28(6):837-41.
9. Mavrelos D, Naftalin J, Hoo W, Ben-Nagi J, Holland T, Jurkovic D. Preoperative assessment of submucous fibroids by three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol 2011 Sep;38(3):350-4.
10. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol 1993 Nov;82(5):736-40.
11. Dueholm M, Lundorf E, Sorensen JS, Ledertoug S, Olesen F, Laursen H. Reproducibility of evaluation of the uterus by transvaginal sonography, hysterosonographic examination, hysteroscopy and magnetic resonance imaging. Hum Reprod 2002 Jan;17(1):195-200.
12. Opolskiene G, Sladkevicius P, Valentin L. Two- and three-dimensional saline contrast sonohysterography: interobserver agreement, agreement with hysteroscopy and diagnosis of endometrial malignancy. Ultrasound Obstet Gynecol 2009 May;33(5):574-82.

13. Nieuwenhuis LL, de Vaate MA, Hehenkamp WJ, Heymans MW, van Baal MW, Brolmann HA, et al. Diagnostic and clinical value of 3D gel installation sonohysterography in addition to 2D gel installation sonohysterography in the assessment of intrauterine abnormalities. Eur J Obstet Gynecol Reprod Biol 2014 Apr;175:67-74.
14. Parsons AK, Lense JJ. Sonohysterography for endometrial abnormalities: preliminary results. J Clin Ultrasound 1993 Feb;21(2):87-95.
15. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 Mar;33(1):159-74.
16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 Feb 8;1(8476):307-10.
17. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999 Jun;8(2):135-60.
18. Emanuel MH. 3D echoscopie van het cavum uteri. Reproductieve geneeskunde, gynaecologie en obstetrie, anno 2009 , 392-395. 2009. Ref Type: Generic
19. Vercellini P, Cortesi I, Oldani S, Moschetta M, De GO, Crosignani PG. The role of transvaginal ultrasonography and outpatient diagnostic hysteroscopy in the evaluation of patients with menorrhagia. Hum Reprod 1997 Aug;12(8):1768-71.
20. Hart R, Molnar BG, Magos A. Long term follow up of hysteroscopic myomectomy assessed by survival analysis. Br J Obstet Gynaecol 1999 Jul;106(7):700-5.
21. Betjes HE, Hanstede MM, Emanuel MH, Stewart EA. Hysteroscopic myomectomy and case volume hysteroscopic myomectomy performed by high- and low-volume surgeons. J Reprod Med 2009 Jul;54(7):425-8.
22. Makris N, Kalmantis K, Skartados N, Papadimitriou A, Mantzaris G, Antsaklis A. Three-dimensional hysterosonography versus hysteroscopy for the detection of intracavitary uterine abnormalities. Int J Gynaecol Obstet 2007 Apr;97(1):6-9.


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

03

Diagnostic and clinical value of 3D gel installation sonohysterography in addition to 2D gel installation sonohysterography in the assessment of intrauterine abnormalities

Lotte L. Nieuwenhuis
Marjolein (A.J.) Bij de Vaate
Wouter J.K. Hehenkamp
Martijn W. Heymans
Marchien (W.M.) van Baal
Hans A.M. Brölmann
Judith A.F. Huirne

Eur J Obstet Gynecol Reprod Biol. 2014 Apr;175:67-74

ABSTRACT

Objective: to study the diagnostic value of three dimensional gel instillation sonography (3D GIS) in addition to two dimensional (2D) GIS in the assessment of intrauterine abnormalities. Secondly, the clinical value of 3D GIS in the planning for hysteroscopic procedures was evaluated.

Study Design: a prospective cohort study was performed from 2008 till 2010. All women with a suspected intra-uterine abnormality on 2D GIS suitable for hysteroscopic resection or with recurrent postmenstrual bleeding were planned for a hysteroscopic procedure. Diagnostic accuracy tests were calculated for the detection of fibroids and polyps with both histology and hysteroscopy as the reference standard. For the assessment of type and size of fibroids hysteroscopy was used as reference standard. We compared the planning for type of hysteroscopy based on 2D GIS findings with the combined 2-3D GIS findings.

Results: in total 110 patients were analysed. In comparison to histology, addition of 3D GIS did not change sensitivity or specificity substantially in the discrimination between fibroids and polyps. In comparison to hysteroscopy sensitivity increased for detecting fibroids and polyps, without major interference of the specificity. Despite an improved accuracy after the addition of 3D GIS, the planning for hysteroscopic procedures did not improve substantially.

Conclusion: In daily practise, the addition of 3D GIS to 2D GIS improved the accuracy for the detection of polyps and fibroids compared to hysteroscopy, but only marginally improved the planning of hysteroscopic procedures, therefore the clinical relevance seems to be limited.

Key words: saline or gel infusion, sonohysterography, three dimensional, abnormal uterine bleeding, intra uterine abnormalities.

INTRODUCTION

Abnormal uterine bleeding affects about 22% of healthy premenopausal women above 35 years of age [1]. Furthermore, abnormal bleeding accounts for almost 25% of gynaecological operations [2]. Apart from hormonal imbalance, intracavitary abnormalities are the leading cause. Intracavitary abnormalities are present in more than 40% of the women who are referred by the general practitioner for abnormal uterine bleeding [3].

Two dimensional *saline infusion* sonohysterography (2D SIS) and 2D *gel instillation* sonohysterography (2D GIS) are techniques for the detection of focally growing intrauterine abnormalities [4;5] and reported to be accurate[5;6]. Three-dimensional (3D) sonography allows the examination of the uterus in any plane (*see figure 1*). It has been reported that 3D SIS is highly accurate in the diagnosis of uterine abnormalities [7-10] and can provide an alternative to hysteroscopy in the diagnostic workup of abnormal vaginal bleeding [11]. In addition, there is good overall agreement between 3D SIS and diagnostic hysteroscopy in classification of submucous fibroids [12]. The advantage of 3D SIS (over 2D SIS) lies in accurate measurement of fibroid size and extent of protrusion of submucous fibroids into the uterine cavity [13-15]. Both parameters are important determinants for the planning of hysteroscopic procedures in terms of applied anaesthetics, used instruments and required level of experience of the surgeon [16]. 3D sonography is reported to be of additional value to 2D sonography in the diagnosis of intracavitary abnormalities [17]. Few studies [7;18] have evaluated the additional value of 3D SIS compared to 2D SIS and reported 3D SIS to be of additional value. The differences were small and not significant. Therefore more data are needed to establish the additional value of 3D SIS over 2D SIS in daily practice and its effect on the planning of hysteroscopic procedures.

The objective of the current study is to evaluate the diagnostic value of 3D GIS in addition to 2D GIS compared with 2D GIS alone in the assessment of intrauterine abnormalities with both hysteroscopy and histology as reference tests. Furthermore, we evaluated the clinical value of 3D GIS in addition to 2D GIS in terms of correct planning (preoperative triage) of therapeutic hysteroscopic procedures.

Figure 1: Intracavitairy abnormality visible at 3 different planes (sagittal plane, transversal plane, coronal plane)

MATERIALS AND METHODS

From January 2008 till January 2010 a prospective cohort study was performed at the Gynaecology Department of the VU medical centre (VUmc) in Amsterdam, the Netherlands.

Women with abnormal uterine bleeding, dysmenorrhoea, recurrent miscarriage, infertility or suspicion for an intrauterine abnormality on regular ultrasound received a 2D GIS. All women with an intrauterine abnormality on 2D GIS (expected to be suitable for hysteroscopic resection) or with an indication for hysteroscopic evaluation because of recurrent postmenstrual bleeding (most frequently in combination with the suspicion of intracavitary pathology), were planned for a hysteroscopy and included in the study. Suspected intra-uterine abnormalities were i.a. polyps, fibroid or an endometrial thickness >4 mm in postmenopausal women. Exclusion criteria were risk of pelvic inflammatory disease, cervical cancer, pregnancy, premenopausal women in the luteal phase without use of contraception. Eight hundred fifty five women received 2D GIS (see figure 2). Hundred and ten women could be analysed, they all underwent a 2D GIS, 3D GIS and hysteroscopy (with histology results). Median time between GIS and hysteroscopy was six and a half weeks (range 0-48 weeks).

2D and 3D GIS

Two dimensional GIS were performed in couples by a gynaecologist or resident together with one of the three ultrasonographers, experienced in 3D sonography. Patients were pre-treated with 500 mg Naproxen 1 day and 1 hour before procedure. An insemination catheter (length 11,5 cm; inner diameter 1.28mm; Repromed®, Zwolle, The Netherlands) was used for intrauterine infusion of Endosgel (Farco-Pharma, Köln, Germany). A syringe was filled with Endosgel, connected to the base of the catheter and the gel was flushed through the catheter to rid it of small amounts of air. The cervix was cleansed

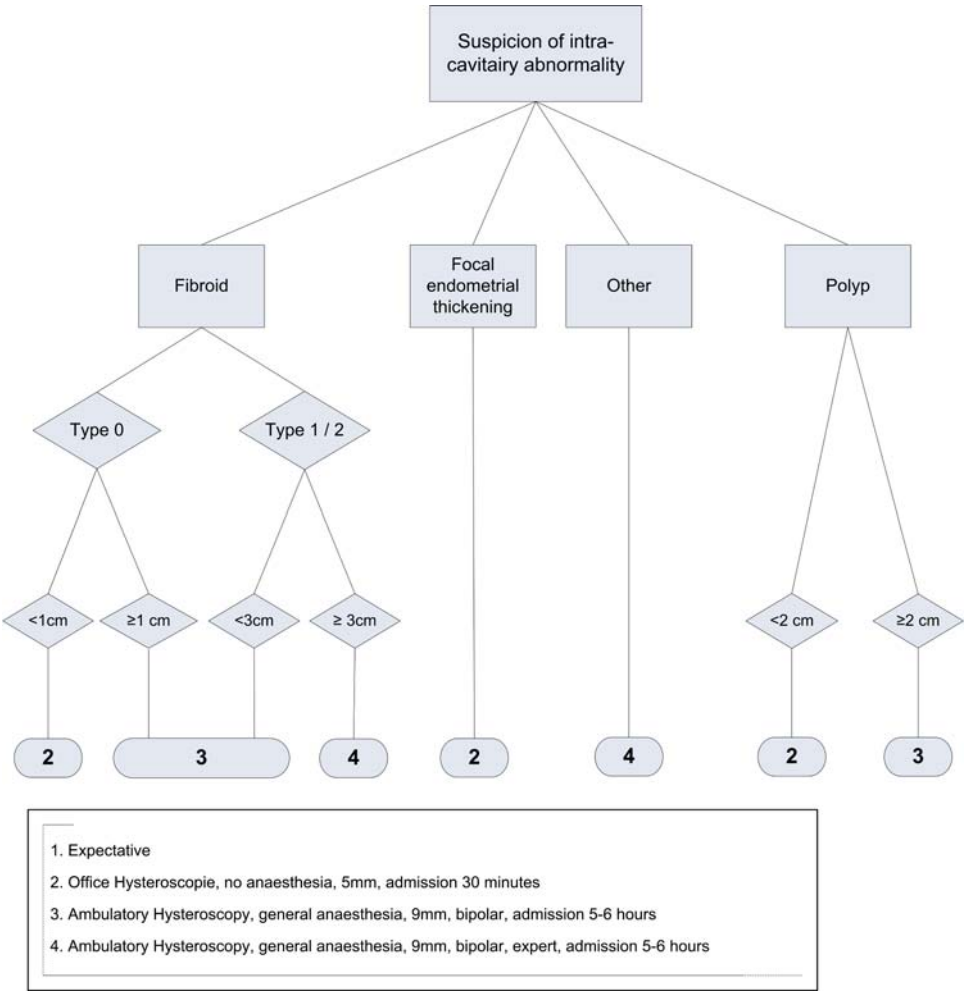


Figure 2: DIMUS study: flow diagram planning for hysteroscopic procedure.

with povidone-iodine solution and the catheter was inserted through the cervical canal with the tip of the catheter just above the internal cervical os. The uterus was filled with gel until the patient felt slight menstrual cramps, backflow was noticed or a maximum of 10 ml was reached. The catheter was removed, the transvaginal transducer (5-8 MHz) introduced and real time 2D ultrasonographic imaging (Accuvix XQ, Medison, Korea) was performed. Image quality and eventual failures of the GIS procedure were registered. In case of an intrauterine abnormality, the sonographer recorded the nature, size and in the case of fibroids percentage of protrusion into the uterine cavity. In addition (the same setting), a 3D volume was generated by an automatic sweep (90

degree angle) of the mechanical transducer performed by one of the three sufficiently trained ultrasonographers, with the ultrasound probe in the midsagittal plane and the uterus within the scan sector. The volumes were all stored digitally as mvl and VOO files. In case of multiple volumes stored for 1 patient, the volume with the most optimal quality was used.

Hysteroscopy

All women underwent a hysteroscopy in a separate setting by a gynaecologist blinded for the 2D and 3D GIS results. In this study, all procedures and reports were performed by or under supervision of one of the four gynaecologists specialized in advanced hysteroscopic resections (total amount of surgeons participating was 10). Duration of procedure, total fluid loss, failures or complications were registered. During hysteroscopy, appearance of the uterine cavity, type and size of uterine abnormalities were registered. In case of a submucous fibroid, the estimated percentage of protrusion into the cavity was based on the angle (<90 degrees type 0 or I; >90 degrees type 2) between the fibroid and the endometrium [15]. In all patients histology was obtained.

Analyses of the 2D examinations and 3D volumes

3D GIS recordings were evaluated by an independent examiner (mbdv), familiar with the interpretation of 3D ultrasound and blinded for the 2D GIS and hysteroscopy findings. The volumes were analysed using multiplanar visualisation (software: 3D XI viewer by Samsung Medison Co). Image quality was scored based on the following aspects: 1) contrast, sharpness and brightness of the image; 2) air bubbles and other artefacts; 3) distension; 4) visualisation in case of an intrauterine abnormality (e.g. contrast around the abnormality, possibility to assess the intracavitary protrusion). The following details of the intrauterine abnormalities (polyps, fibroids, adhesions, septa, others) were registered: location, origin, size and protrusion into the uterine cavity. Smoothly margined echogenic masses with a homogenous texture were classified as polyps, while structures of mixed echogenicity disrupting the endometrial continuity were described as submucous fibroids [19]. Intrauterine fibroids were classified (according tot the classification of the ESGE) into subtypes according to the degree of protrusion into the uterine cavity (type 0 100% intracavitary, type 1 >50% protrusion into the cavity, type 2 <50% protrusion into the cavity). Protrusion was measured as described by Lee et al [13] (*see figure 3*).

Figure 3: Measuring protrusion with 3D GIS. A. protrusion into the cavity, B. part of the fibroid in the myometrium. Fibroid protrusion into the cavity is calculated using (A/ (A+B) x100).

The planning for hysteroscopy

Planning for hysteroscopic procedure was based on the nature and size of the suspected abnormality during real time 2D-GIS according to strict criteria (see figure 4). To evaluate the additional value of 3D GIS in the correct planning of the hysteroscopic procedure, we made a virtual planning (retrospectively) based on the combined 2D+3D results. If 3D GIS had poor image quality and 2D GIS good image quality, the 2D results were used. We evaluated the total number of hysteroscopic procedures that would have been planned differently in case 2D+3D images would have been the base for the planning of the procedure in stead of the 2D-GIS only in terms of chosen setting (ambulatory, office), used instrument (5 or 9 mm scope) and the selection of the surgeon (general gynaecologist; expert gynaecologist). The hysteroscopic results were used as a reference.

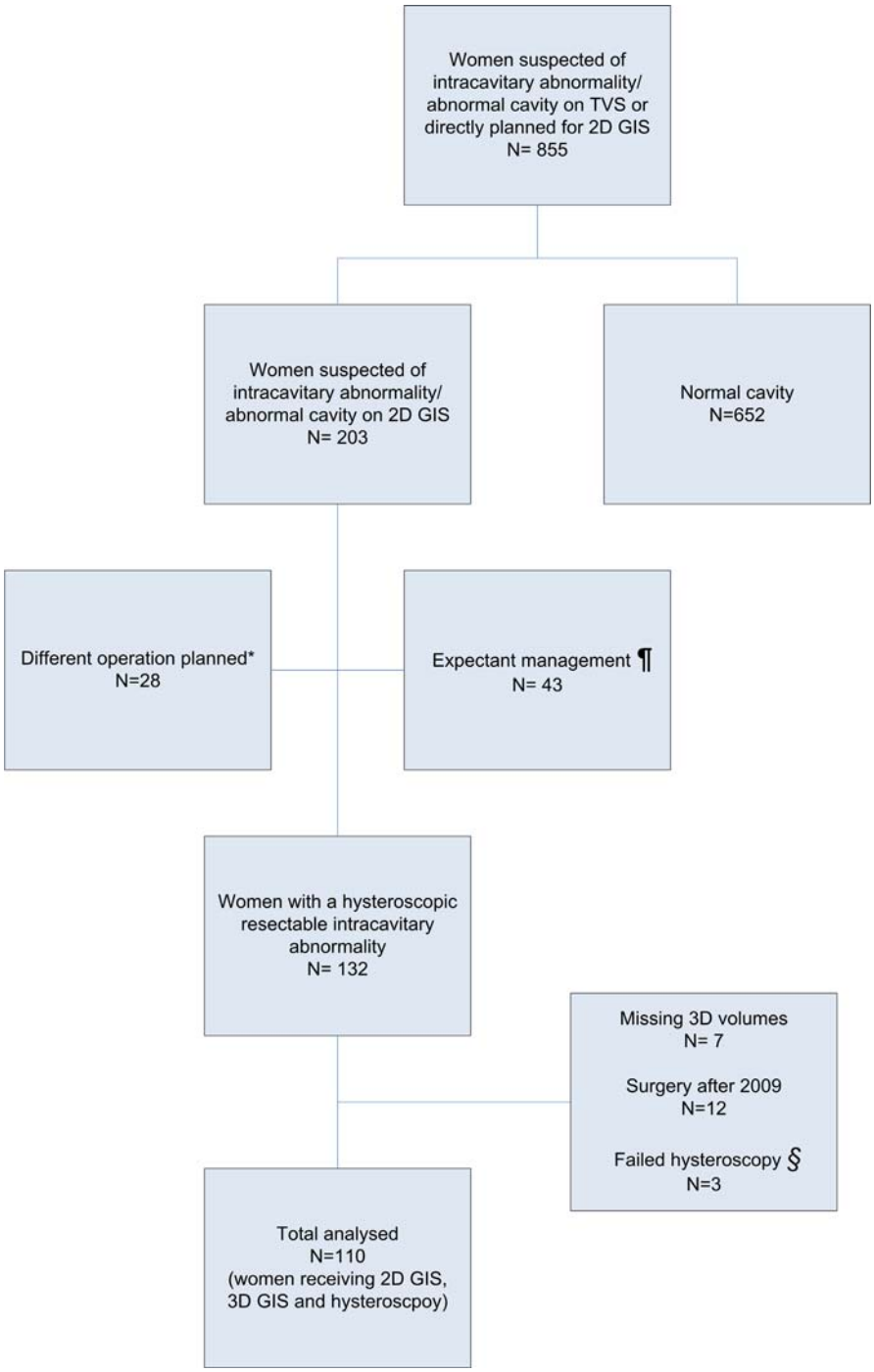


Figure 4: DIMUS study: Flow diagram inclusion

Statistical analysis

The sensitivity, specificity, positive- and negative predictive values and accuracy for the detection of fibroids and polyps were calculated for 2D GIS, 3D GIS, 2+3D GIS with both hysteroscopy and histology as reference tests.

The agreement in classification (none, polyp, fibroid, other) of intrauterine abnormalities between findings of 2D and 2+3D GIS compared to histology results were tested with Cohen's Kappa coefficient. Agreement in type of submucous fibroid, based on percentage of protrusion was tested with hysteroscopy as a reference.

Cohen's Kappa was defined as the difference between observed and expected agreement (by chance), expressed as a fraction of the maximum possible difference. A kappa value of <0.20 indicates slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement [20].

Intraclass correlation coefficient on basis of a two-way mixed ANOVA model and opting for absolute agreement were used to calculate inter-observer agreement for the percentage of protrusion into the uterine cavity of submucous fibroids. ICC values were interpreted similar as the Cohen's Kappa Coefficient.

We calculated the number of hysteroscopy's that would have been planned differently based on 2D+3D GIS with hysteroscopy findings as a reference.

All statistical analyses were performed with SPSS 17 and R software.

RESULTS

Baseline characteristics are listed in table 1. The most commonly diagnosed abnormalities were polyps and fibroids (see table 2).

Table 1. Baseline characteristics

TOTAL NUMBER OF PATIENTS	N=110
Mean age in years (SD)	43.5 (9.6)
Pre menopausal	96 (87%)
Indication for GIS	
Abnormal uterine bleeding	53 (86%)
Infertility	15 (14%)
Medication use	
None	54 (49%)
Oral Contraceptives	23 (20%)
Other (Progestagens, IUD, GnRH agonist)	33 (31%)
Uterine surgical interventions in the history	
None	61 (55 %)
Yes, type:	49 (45%)
Dilatation and curettage	33 (30%)
Transcervical resection of polyps or fibroid	11 (10.5%)
Enucleation of fibroid	5 (4.5%)

Thirty five percent (n= 32) of the 3D volumes were scored as "poor quality". Two of the 110 GIS procedures failed (for both 2D and 3D). Four out of the 110 *3D GIS* volumes were unable to assess due to poor distension. At 2D GIS only single abnormalities were seen. In 3 cases both a fibroid and a polyp were reported on 3D GIS. At hysteroscopy the existence of a fibroid and polyp were confirmed in 2 cases. In the other case, 2 polyps were reported during hysteroscopy which was confirmed by histology.

Hysteroscopy results

In 11 patients no intracavitary abnormalities were found during hysteroscopy. In 76 cases resection was complete, in 17 cases resection was incomplete (in all cases it concerned a large (>3cm) type 1 or 2 fibroid or multiple abnormalities).

Table 2. Type of abnormalities using 2D GIS, 3D GIS, hysteroscopy and histology

	2D GIS	2D+3D GIS	HYSTEROSCOPY	HISTOLOGY
Type of abnormality	N (%)	N (%)	N (%)	N (%)
Polyp	48 (44)	50 (45)	48 (44)	39 (35.5)
Sessile	31 (28.2)	45 (40.9)	26 (21.8)	-
Pedunculated	5 (4.5)	5 (4.5)	14 (12.7)	-
Unknown type	12 (10.9)	0	10 (9.1)	-
Fibroid	45 (41)	45 (41)	43 (39)	46 (41.8)
type 0	13 (11.8)	9 (8.2)	8 (7.3)	-
type 1	18 (16.4)	12 (10.9)	21 (19.1)	-
type 2	10 (9.1)	23 (20.9)	14 (12.7)	-
unknown type	4 (3.6)	1 (0.9)	0	-
Adhesions/synechiae	3 (2.7)	2 (1.8)	2 (1.8)	0 (0)
Focal endometrium thickening	1 (0.9)	1 (0.9)	2 (1.8)	3 (2.7)
Other *	6 (5.5)	6 (5.5)	3 (2.7)	4 (3.6)
Unclear **	2 (1.8)	2 (1.8)	0	4 (3.6)
Normal cavity	5 (4.5)	4 (3.6)	12 (11)	14 (12.7)
Total number (%)	110 (100)	110 (100)	110 (100)	110 (100)

*'Other' is defined as other diagnose; placental rest, blood clots, niche

** 'Unclear' was when ultrasound image could not be evaluated (due to very poor quality) or too little tissue was collected (during hysteroscopy) for a proper histology result

Additional value of 3D GIS using *histology* as a reference

The sensitivity and specificity are listed in table 3a. The Cohen's kappa coefficient for agreement in classification of intrauterine abnormalities (none, polyp, fibroid, other) between 2D GIS and histology was 0.67 (CI 0.55-0.78), between 2-3D GIS and histology 0.61 (CI 0.49-0.72). If we exclude the volumes with poor quality Cohen's kappa improved slightly, respectively 0.67 (CI 0.5-0.8) for 2D-GIS and histology and 0.68 (CI 0.54-0.82) for 2-3D-GIS and histology.

Additional value of 3D GIS using *hysteroscopy* as a reference

Results are listed in table 3b). The Cohen's kappa coefficient for agreement in classification of intrauterine abnormalities (none, polyp, fibroid, other) between 2D GIS and hysteroscopy was 0.72 (CI 0.62-0.83) and between 2-3D GIS and hysteroscopy was 0.70 (0.59-0.80). If we exclude the volumes with 'poor quality' Cohen's kappa improved slightly, respectively 0.73 (CI 0.59-0.87) and to 0.82 (CI 0.70-0.93).

Classification of submucous fibroids

The Cohen's Kappa value for the agreement on type of fibroid (0, I, II) between 2D and hysteroscopy was poor (0.31, CI 0.07-0.55). Kappa was 0.41 (CI 0.2-0.6) for 3D versus hysteroscopy, and 0.31 (CI 0.1-0.5) between 2D-3D GIS hysteroscopy. ICC values were better (moderate) for the % of protrusion. Between 2D and hysteroscopy ICC was 0.52 (CI 0.19-0.75) and for 3D and hysteroscopy ICC was 0.53 (CI 0.2-0.75).

Planning for type of hysteroscopy

Based on 2D GIS results, 6 patients were planned for expectant management, 47 patients for office procedure (5mm scope) and 57 for ambulatory procedure with anaesthetics (9mm scope, of whom 8 patients were planned with an expert).

The addition of 3D GIS to 2D GIS would have resulted in a reduction of incorrect expectant management in 2 cases and incorrect planning of ambulatory hysteroscopy without an expert in 3 casus (table 4). Thus it would have reduced insufficient planning of treatment in 5 cases.

On the other hand it would have resulted in an increase of unneeded treatment in 4 cases. One case of unneeded scheduling of an expert, in 2 patients the use of anaesthetics could have been avoided and in 1 patient an operation could have been avoided.

37% Percent of the hysteroscopy's were incorrectly planned using 2D GIS. Moreover 12 out of 17 (71%) expert hysteroscopy's were not correctly planned based on 2D GIS. 3D GIS improved planning; 3 patients were planned for a surgeon with appropriate expertise.

Table 3a. diagnostic accuracy of two- and three dimensional gel installation sonohysterography (2D GIS, 3D GIS) for the detection of fibroids and polyps with **histology** as a reference

	2D GIS	3D GIS	2D+3D GIS
Number of patients	110	110	110
Fibroids			
Sensitivity % (95%CI)	89 (76-96)	91 (79-98)	91 (79-98)
Specificity	93 (84-98)	91 (81-97)	93 (84-98)
PPV	91 (78-97)	89 (76-96)	91 (79-98)
NPV	92 (82-97)	93 (83-98)	94 984-98)
Accuracy	92 (84-96)	91 (84-96)	93 (86-97)
Polyps			
Sensitivity	85 (70-94)	80 (64-92)	84 (69-94)
Specificity	79 (68-88)	74 (62-84)	77 (66-86)
PPV	69 (54-81)	63 (48-77)	67 (52-80)
NPV	90 (80-96)	88(76-95)	90 (80-96)
Accuracy	81 (72-88)	77 (67-84)	80 (71-87)

Table 3b. diagnostic accuracy of two- and three dimensional gel installation sonohysterography (2D GIS, 3D GIS) for the detection of fibroids and polyps with **hysteroscopy** as a reference

	2D GIS	3D GIS	2D+3D GIS
Number of patients	110	110	110
Fibroids			
Sensitivity % (95%CI¶)	95 (84-99)	95 (84-99)	98 (88-100)
Specificity	94 (85-98)	90 (80-96)	94 (85-98)
PPV	91 (79-98)	87 (74-96)	91 (79-98)
NPV	97 (89-100)	96 (88-100)	98 (91-100)
Accuracy	94 (88-98)	92 (85-97)	95 (90-99)
Polyps			
Sensitivity	83 (69-92)	86 (73-95)	89 (76-96)
Specificity	87 (76-94)	86 (75-94)	89 (78-95)
PPV	83 (69-92)	83 (69-92)	85 (72-94)
NPV	87 (76-94)	89 (78-96)	92 (81-97)
Accuracy	86 (77-91)	86 (78-92)	89 (81-94)

¶ 95%CI: 95% confidence interval.

Table 4. Number of correctly planned hysteroscopy's (retrospective virtual planning) for 2D GIS and 2D+3D GIS using hysteroscopy results as a reference test

RESULTS BASED ON HYSTEROSCOPY		PLANNING BASED ON 2D GIS RESULTS		PLANNING BASED ON 2D+3D GIS	
(Reference test)	**N**	**Correct**	**Incorrect**	**Correct**	**Incorrect**
Expectative management (EM)	13	4 EM	9 OH	3 EM	10 OH
Office hysteroscopy* *(OH)*	38	29 OH	9 (2 EM, 7 AH)	29 OH	9 AH
Ambulatory hysteroscopy *(AH)¶*	42	31 AH	11 (8 OH, 3 expert)	30 AH	12 (8 OH, 4 expert)
Ambulatory with expert (expert)	17	5 expert	12 AH	8 expert	9 AH
Total	110	69	41	70	40

*Office hysteroscopy was performed without the use of anaesthetics.

¶ Ambulatory hysteroscopy was performed with anaesthetics.

COMMENT

Main findings

With hysteroscopy as reference test, the addition of 3D GIS to 2D GIS in daily practise improved sensitivity for both fibroids and polyps without effecting with specificity, whereas no improvements on test characteristics were demonstrated when compared to histology. The level of agreement in the percentage of protrusion into the uterine cavity of submucous fibroids between hysteroscopy and 2D GIS, 3D GIS and 2-3D GIS may all be considered as moderate. Only marginal improvement in correct planning of hysteroscopic procedures was found after the addition of 3D GIS tot 2D GIS. Results of 3D GIS must be interpreted with caution considering the high number of poor 3D examinations that were found.

Strengths and limitations of the study

Study design for a clinical study on diagnostic test accuracy is challenging. We chose to use both hysteroscopy and histology as a reference to obtain the best possible reference test. Both have their own limitations. Although histology is mostly considered as a golden standard, histology does not provide any useful information in the classification of submucous fibroids and specimens are dependent on the location of taken biopsies. Hysteroscopy can provide information to classify submucous fibroids but the level of

fibroid protrusion might be influenced by the applied intra-uterine pressure. In addition, hysteroscopy can underestimate protrusion (lack of vision) but can also overestimate when procedure is difficult to perform. Subjectivity in the judgment cannot be excluded and therefore includes the risk on bias. For example, one expert may rate the procedure as easy while another expert may have rated the procedure as requiring an expert. Variation in the classification of the difficulty of the procedure between observers could have been prevented by blinded and objective evaluation by one independent observer using video recordings of the procedure. Mavrelos et al [14] also stated that hysteroscopy cannot be used to measure the size of the fibroid or its component confined to the myometrium accurately. The 3D GIS assessment was performed by an independent observer unaware of the hysteroscopic or 2D GIS findings in order to reduce verification bias. A limitation is that the majority of patients with a normal uterine cavity on 2D GIS were not included in the study. Therefore the calculation of the negative predictive value (NPV) of a normal 2D GIS was only based on a few women with recurrent postmenstrual bleeding. Secondly it is difficult in such a setting for 3D GIS to increase the sensitivity, as patients are selected based on abnormal findings at 2D GIS, and thereby missed cases at 2D GIS cannot be found at 3D GIS.

Given the reported negative predictive value of 2D GIS of around 96% [7] we assumed that the total number of patients that did not receive a hysteroscopy with an undetected intra-uterine abnormality may be considered as minimal. Another limitation may have been the performance of 3D GIS. Gel was added before entering the probe, which may lead to insufficient distension in some cases. This might be an explanation for the relatively high number of 'poor quality' images. Distension and related image quality may be improved by installing the gel under sonographic guidance.

Interpretation of the findings

Our results are in agreement with previous studies that reported high accuracy for 3D sonohysterography [7;8;10-12;21;22]. However most of these studies were performed in an ideal research setting in which 3D sonography was performed by one experienced researcher. Most studies did not study the clinical relevance in daily practice and whether 3D sonohysterography improved preoperative triage. Preoperative patient selection and planning is critical for the success of hysteroscopic procedures [14]. Studies evaluating the benefit of 3D GIS on pre-operative triage are lacking. De Kroon et al [7] reported that 3 out of 45 patients would have had a benefit of additional 3D sonohysterography in preventing unneeded hysteroscopy and concluded that 3D sonohysterography is of clinical value. In our study, the benefit of 3D SIS was marginal. The lowest agreement between 2D-3D and hysteroscopic evaluation was observed in

the classification of submucous fibroids, which is probably one of the most important determinants for hysteroscopic planning [14;15;23]. The number of incorrectly planned hysteroscopy's was high and even higher when an expert was needed. De Kroon found similar results and reported that in 6 out of 22 (= 27%) cases, hysteroscopic findings did not correspond with findings on 3D SIS. Both underestimation and overestimation contribute to the incorrectly planned hysteroscopy's. Underestimation seems to be less with the additional of 3D SIS and in our study 3D SIS slightly improved the planning of more advanced hysteroscopic procedures.

Future studies

Our study results underline the need for an RCT to study the additional value of 3D GIS to 2D GIS on the total number of incomplete resections and unneeded exposure to general anaesthetics. In such a study most ideally two strategies should be compared: using 2D GIS in the control and using the combined real time 2D and 3D GIS in the intervention arm, with cost-effectiveness alongside and a special focus on pre-operative planning.

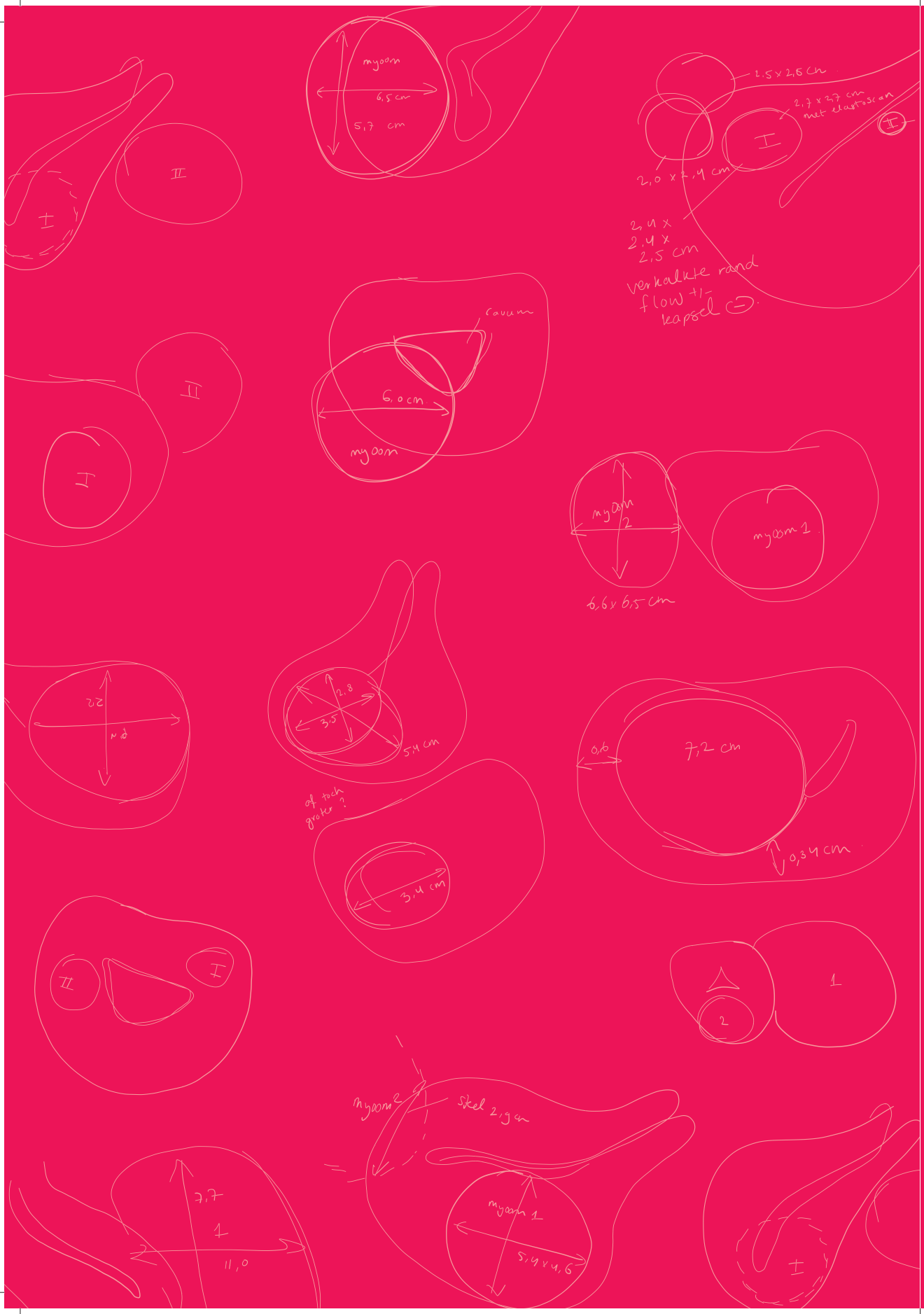
In conclusion, the addition of 3D to 2D GIS in daily practice improved the accuracy (and equals the diagnostic accuracy of hysteroscopy and histology) for the detection of polyps and fibroids. The addition of 3D GIS to 2D GIS did not give a substantial improvement in the planning of hysteroscopic procedures.

REFERENCES

1. Gath D, Osborn M, Bungay G, Iles S, Day A, Bond A, et al. Psychiatric disorder and gynaecological symptoms in middle aged women: a community survey. Br Med J (Clin Res Ed) 1987 Jan 24;294(6566):213-8.
2. Goldstein SR. Menorrhagia and abnormal bleeding before the menopause. Best Pract Res Clin Obstet Gynaecol 2004 Feb;18(1):59-69.
3. Emanuel MH, Verdel MJ, Wamsteker K, Lammes FB. A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding: clinical implications. Am J Obstet Gynecol 1995 Feb;172(2 Pt 1):547-52.
4. Bij de Vaate AJ, Brolmann HA, van der Slikke JW, Emanuel MH, Huirne JA. Gel instillation sonohysterography (GIS) and saline contrast sonohysterography (SCSH): comparison of two diagnostic techniques. Ultrasound Obstet Gynecol 2010 Apr;35(4):486-9.
5. de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG 2003 Oct;110(10):938-47.
6. van Dongen H, de Kroon CD, van den Tillaart SA, Louwe LA, Trimbos-Kemper GC, Jansen FW. A randomised comparison of vaginoscopic office hysteroscopy and saline infusion sonography: a patient compliance study. BJOG 2008 Sep;115(10):1232-7.
7. de Kroon CD, Louwe LA, Trimbos JB, Jansen FW. The clinical value of 3-dimensional saline infusion sonography in addition to 2-dimensional saline infusion sonography in women with abnormal uterine bleeding: work in progress. J Ultrasound Med 2004 Nov;23(11):1433-40.
8. Abou-Salem N, Elmazny A, El-Sherbiny W. Value of 3-dimensional sonohysterography for detection of intrauterine lesions in women with abnormal uterine bleeding. J Minim Invasive Gynecol 2010 Mar;17(2):200-4.
9. Khan F, Jamaat S, Al-Jaroudi D. Saline infusion sonohysterography versus hysteroscopy for uterine cavity evaluation. Ann Saudi Med 2011 Jul;31(4):387-92.
10. Sylvestre C, Child TJ, Tulandi T, Tan SL. A prospective study to evaluate the efficacy of two- and three-dimensional sonohysterography in women with intrauterine lesions. Fertil Steril 2003 May;79(5):1222-5.
11. Makris N, Kalmantis K, Skartados N, Papadimitriou A, Mantzaris G, Antsaklis A. Three-dimensional hysterosonography versus hysteroscopy for the detection of intracavitary uterine abnormalities. Int J Gynaecol Obstet 2007 Apr;97(1):6-9.
12. Salim R, Lee C, Davies A, Jolaoso B, Ofuasia E, Jurkovic D. A comparative study of three-dimensional saline infusion sonohysterography and diagnostic hysteroscopy for the classification of submucous fibroids. Hum Reprod 2005 Jan;20(1):253-7.

13. Lee C, Salim R, Ofili-Yebovi D, Yazbek J, Davies A, Jurkovic D. Reproducibility of the measurement of submucous fibroid protrusion into the uterine cavity using three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol 2006 Nov;28(6):837-41.
14. Mavrelos D, Naftalin J, Hoo W, Ben-Nagi J, Holland T, Jurkovic D. Preoperative assessment of submucous fibroids by three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol 2011 Sep;38(3):350-4.
15. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol 1993 Nov;82(5):736-40.
16. Betjes HE, Hanstede MM, Emanuel MH, Stewart EA. Hysteroscopic myomectomy and case volume hysteroscopic myomectomy performed by high- and low-volume surgeons. J Reprod Med 2009 Jul;54(7):425-8.
17. Benacerraf BR, Shipp TD, Bromley B. Which patients benefit from a 3D reconstructed coronal view of the uterus added to standard routine 2D pelvic sonography? AJR Am J Roentgenol 2008 Mar;190(3):626-9.
18. Kowalczyk D, Guzikowski W, Wiecek J, Sioma-Markowska U. Clinical value of real time 3D sonohysterography and 2D sonohysterography in comparison to hysteroscopy with subsequent histopathological examination in perimenopausal women with abnormal uterine bleeding. Neuro Endocrinol Lett 2012;33(2):212-6.
19. Parsons AK, Lense JJ. Sonohysterography for endometrial abnormalities: preliminary results. J Clin Ultrasound 1993 Feb;21(2):87-95.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 Mar;33(1):159-74.
21. La Torre R, De FC, De AC, Coacci F, Mastrone M, Cosmi EV. Transvaginal sonographic evaluation of endometrial polyps: a comparison with two dimensional and three dimensional contrast sonography. Clin Exp Obstet Gynecol 1999;26(3-4):171-3.
22. Terry S, Banks E, Harris K, Duvivier R, Dar P. Comparison of 3-dimensional with 2-dimensional saline infusion sonohysterograms for the evaluation of intrauterine abnormalities. J Clin Ultrasound 2009 Feb 10.
23. Emanuel MH. 3D echoscopie van het cavum uteri. Reproductieve geneeskunde, gynaecologie en obstetrie, anno 2009 , 392-395. 2009.

Ref Type: Generic


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

04

Cochrane review: Three-dimensional compared to two-dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions of the uterus

Lotte L Nieuwenhuis
Frederik JR Hermans
A J Marjolein Bij de Vaate
Mariska MG Leeflang
Hans AM Brölmann
Wouter JK Hehenkamp
Ben Willem J Mol
T Justin Clark
Judith AF Huirne

Cochrane Database Syst Rev. 2017 May 5;5:CD011126

ABSTRACT

Background: Focal abnormalities most commonly acquired within the uterine cavity include endometrial polyps (arising from the endometrium) and submucous fibroids (arising from the myometrium). These benign abnormalities can cause several problems, including abnormal uterine bleeding (AUB) and subfertility. Two-dimensional saline infusion sonography (2D SIS) is a minimally invasive test that can be used to diagnose these pathologies, but it is less accurate than hysteroscopy, which is a more invasive procedure by which an endoscope allows direct visualisation of the uterine cavity. Three-dimensional (3D) SIS appears to enhance sonographic visualisation within the uterine cavity, thereby offering a potentially more accurate minimally invasive diagnostic test.

Objectives

Primary objectives

• To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS for the diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test.

• To evaluate the diagnostic accuracy of 2D+3D SIS (index test 2) compared with 2D SIS for the diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test. In this case, any abnormality on either modality was regarded as a positive result ('OR' approach).

Secondary objectives

• To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS according to type of abnormality and discrimination between uterine polyps and submucous fibroids in women with AUB or subfertility, with hysteroscopy and histology used as the reference.

• To evaluate the diagnostic accuracy of 2D+3D SIS (index test 2) compared with 2D SIS according to type of abnormality and discrimination between uterine polyps and submucous fibroids in women with AUB or subfertility, with hysteroscopy and histology used as the reference.

Search methods: We searched the following databases: Cochrane Central Register of Studies Online (CENTRAL CRSO), MEDLINE, Embase, PubMed, Cochrane Gynaecology and Fertility Group (CGF) Specialised Register and CGFG Diagnostic Test Accuracy (DTA) Specialised Register, clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Screening reference lists of

appropriate studies was also performed. We screened for eligibility all studies identified from inception until March 2016. We performed searches with no date or language restrictions.

Selection criteria: The population of interest consisted of premenopausal women with AUB or subfertility and postmenopausal women with AUB. Diagnostic test accuracy studies, randomised controlled trials (RCTs) and prospective cohort studies were eligible for inclusion if they evaluated the accuracy of both 2D SIS and 3D SIS for the diagnosis of acquired intracavitary abnormalities with hysteroscopy used as the reference standard. In light of the lack of data for 3D SIS, we also included studies that evaluated the accuracy of 3D SIS alone.

Data collection and analysis: Two review authors read all potentially eligible references after performing a first screening by title and abstract (LLN and FJRH). They independently extracted data to construct 2×2 tables from eligible studies and assessed studies for methodological quality using the QUADAS-2 tool (revised tool for quality assessment of diagnostic accuracy studies). To describe and visually present results, we produced in RevMan forest plots showing pairs of sensitivity and specificity together with 95% confidence intervals from each study, as well as raw receiver operating characteristic (ROC) plots. We displayed paired analyses in an ROC plot by linking sensitivity-specificity pairs from each study by using a dashed line. To compare 3D SIS versus 2D SIS, we restricted analyses to studies that provided 2×2 tables for both tests and used the bivariate meta-analysis of sensitivity and specificity.

Main results: Thirteen studies (1053 women) reported the accuracy of 3D SIS for focal uterine abnormalities; 11 of these (846 women) were suitable for meta-analysis, and eight reported accuracy according to the type of focal abnormality. The design of the included studies seems applicable. The main problem involving the quality of included studies is insufficient reporting of study methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, we considered the overall quality of the evidence as low. The summary estimate (11 studies reporting absence or presence of abnormality at 3D SIS) for sensitivity was 94.5% (95% confidence interval (CI) 90.6% to 96.9%) and for specificity 99.4% (95% CI 96.2% to 99.9%). Meta-analysis of the eight studies (N = 716) directly comparing 2D SIS versus 3D SIS showed summary sensitivity of 96.9% (95% CI 91.9% to 98.8%) and summary specificity of 99.5% (95% CI 96.1% to 100%) for 3D SIS. For 2D SIS, summary sensitivity was 90.9% (95% CI 81.2% to 95.8%) and summary specificity was 96.3% (95% CI 86.1% to 99.1%). The difference in accuracy between 2D SIS and 3D SIS was non-significant (P values of 0.07 for sensitivity and 0.10 for specificity).

Authors' conclusions: Low-quality evidence suggests that 3D SIS may be very accurate in detecting intracavitary abnormalities. Meta-analysis revealed no statistically significant differences between 2D SIS and 3D SIS. Summary sensitivity and summary specificity are higher for 3D SIS, but margins of improvement are limited because 2D SIS is already very accurate. When the technology and appropriate expertise are available, 3D SIS offers an alternative to 2D SIS. Both 2D SIS and 3D SIS should be considered alternatives to diagnostic hysteroscopy when intracavitary pathology is suspected in subfertile women and in those with abnormal uterine bleeding.

PLAIN LANGUAGE SUMMARY

Review question

Is three-dimensional saline infusion sonography (3D SIS) better than two-dimensional (2D) SIS for detecting polyps and fibroids?

Background

The womb (uterus) is one of the female reproductive organs. Inside the cavity of the womb, abnormalities such as polyps and fibroids can grow. Polyps and fibroids can cause problems such as abnormal menstrual bleeding and difficulty getting pregnant. The presence of these polyps and fibroids may be a reason for clinicians to start drug therapy or remove the polyps and fibroids during surgery.

Ultrasonography can provide a picture of the womb and of possible fibroids or polyps. Saline or gel inside the cavity of the womb makes the ultrasound image more clear. This technique is called saline infusion sonography (SIS). Usually, this picture is only two-dimensional. Nowadays, it is possible to make a three-dimensional picture so the type of abnormality can be better seen.

Study characteristics

Review authors searched for studies published from inception until March 2016 and found 13 studies (in total 1053 women), eight of which directly compared 3D SIS versus 2D SIS. Data included all women reporting abnormal menstrual bleeding or difficulty getting pregnant. The number of patients in these studies varied from 23 to 180 women.

Quality of the evidence

In all studies, researchers checked the results of 2D SIS and 3D SIS against results obtained when a camera was used to look inside the womb (hysteroscopy); this is expected to give the true picture but is also more painful for the patient. All studies were performed in the usual way. Some studies did not report several items that might have influenced the results. For example, not all studies made it clear that the person evaluating the ultrasound pictures was unaware of the hysteroscopy results, and vice versa. The main problem involving the quality of included studies is insufficient reporting of study methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, review authors considered the overall quality of the evidence as low.

Key results

Low-quality evidence suggests that 3D SIS may be very accurate in detecting polyps and fibroids. Our analysis revealed no clear differences between 2D SIS and 3D SIS. Summary results are higher for 3D SIS but margins of improvement are limited because 2D SIS is already very accurate. Results show that 2D SIS missed a fibroid or polyp in 9 of 100 women and 3D SIS missed a polyp or fibroid in 3 of 100 women who had them. In 4 of 100 women, 2D SIS indicated the presence of polyps or fibroids when there were none, and in less than 1 in 100 women, 3D SIS was wrong. In theory, if both tests were used in a group of 1000 women with abnormal menstrual bleeding, 300 with fibroids or polyps, 27 of the 300 women with polyps/fibroids will be missed by 2D SIS, and 9 of 300 will be missed by 3D SIS.

3D SIS is an alternative to 2D SIS for which the technology and appropriate expertise are available. Both 2D SIS and 3D SIS should be considered alternatives to diagnostic hysteroscopy when intracavitary pathology is suspected in subfertile women and in those with abnormal uterine bleeding.

BACKGROUND

Target condition being diagnosed

The most common focal intracavitary uterine abnormalities are acquired benign formations arising from the endometrium (endometrial polyps) or from the underlying myometrium (submucous fibroids). These abnormalities are important because they are thought to cause abnormal uterine bleeding (AUB) and subfertility (Golan 2001; Klatsky 2008; Munro 2011; Pritts 2009). It is unclear how focal disruption of the endometrial lining and uterine cavity causes AUB and subfertility. In the case of submucous fibroids, AUB is thought to arise through enlargement of the endometrial surface or as the result of bleeding from stretched and fragile blood vessels (Patterson 1994; Stewart 1996).

Abnormal uterine bleeding affects about 10% to 35% of healthy premenopausal women (Gath 1987; Liu 2007; Santer 2005). Apart from hormonal imbalance, intracavitary abnormalities are the leading cause (Emanuel 1995; Tur-Kaspa 2006; Werbrouck 2011). Postmenopausal bleeding (PMB) is less common than AUB but should always be evaluated to rule out endometrial carcinoma or endometrial hyperplasia. Polyps and submucous fibroids are common in both premenopausal and postmenopausal women, although polyps appear to be more prevalent and submucous fibroids less prevalent in women of post-reproductive age than in those of reproductive age. In a prospective study of more than 1000 women with AUB, 18.4% of premenopausal versus 37.7% of postmenopausal women were diagnosed with polyps, and 14.2% versus 6.2% showed intracavitary fibroids, respectively (van den Bosch 2015). These focal lesions are also highly prevalent in women with subfertility. In a Cochrane review, the overall prevalence of intracavitary abnormalities in women before in vitro fertilisation (IVF) or intracytoplasmic sperm insemination (ICSI) was 11% (Fatemi HM 2010).

Endometrial polyps and submucous fibroids can be diagnosed via transvaginal sonography (TVS). Saline infusion sonography (SIS) is a sonographic technique whereby saline is instilled through the cervical canal and into the uterine cavity during TVS to distend the uterine cavity, thereby enhancing visualisation. Gel can be used as an alternative distension fluid to saline (GIS). Hysteroscopy is an endoscopic procedure whereby the uterine cavity is visualised directly; it is considered the gold standard for detecting polyps and submucous fibroids (Tarneja 2002). Diagnoses obtained during hysteroscopy are more accurate than those obtained by hysteroscopy with histology in both premenopausal and postmenopausal women (Metello 2008; van Dongen 2007). However, hysteroscopy is considered a more invasive diagnostic modality than TVS or SIS and may require use of a general anaesthetic.

Index test(s)

During saline infusion sonography, fluid (saline or gel) is instilled transcervically into the uterine cavity to provide enhanced visualisation of the endometrial lining during TVS examination.

Two-dimensional saline infusion sonography (2D SIS) and diagnostic hysteroscopy are techniques used for detection of intrauterine abnormalities (Dijkhuizen 2003). Both SIS and GIS are simple, safe, well tolerated and accurate for assessment of intrauterine abnormalities (Beemsterboer 2008; Bij de Vaate 2010). Although 2D SIS has become the diagnostic test of choice in most clinical practices, diagnostic hysteroscopy (with histology) remains the gold standard to confirm the presence or absence of an intrauterine abnormality.

Three-dimensional (3D) SIS enhances visualisation of the uterine cavity and is reported to be highly accurate (Abou Salem 2010; Lee 2006; Salim 2005; Terry 2009). Three-dimensional SIS allows examination of the uterus from any angle and in any plane, and this allows the examiner to more precisely measure fibroid size and the extent of protrusion of submucous fibroids into the uterine cavity. This procedure can be performed during the same session as 2D SIS, and the procedure is similar, apart from the requirement that a 3D ultrasonic probe be used. The duration of performing 3D SIS is similar to that for 2D SIS. In 3D SIS, a video can be stored and (re-)studied at any time and in any plane at the ultrasonography machine or on a personal computer. As 3D SIS is reported to be accurate, it may provide additional value over 2D SIS, or may even replace it.

This review focused on studies in which 3D SIS (index test 1) and 2D SIS+3D SIS (index test 2) were compared with 2D SIS (comparator test), using hysteroscopy as the reference test, to identify acquired intrauterine abnormalities, polyps and submucous fibroids. When possible, 3D SIS was compared with 2D SIS according to type of abnormality (i.e. to differentiate between polyps and submucous fibroids) with hysteroscopy and histology as the reference test.

Clinical pathway

In most clinics in developed countries, women with AUB or subfertility undergo TVS. When an intracavitary abnormality on TVS is suspected, a 2D SIS can be planned to diagnose presence, size and type of abnormality (Guideline ACOG; Guideline NVOG; Guideline SOGC). Although hysteroscopy is a relatively safe operation associated with minor complications, it is more expensive and burdensome for the patient than is SIS

(Dijkhuizen 2003; Dongen 2011; van den Bosch 2008; Widrich 1996). The main reason it is more burdensome is that it is reported to be more painful than SIS and sometimes requires the use of general anaesthesia.

If an intracavitary abnormality is seen during 2D SIS, a treatment plan can usually be made that involves scheduling an operative hysteroscopic procedure at the point where the abnormality will be resected or morcellated in an outpatient clinic (most polyps) or in a hospital day care setting with the patient under regional or general anaesthesia (most submucous fibroids).

If a normal cavity is seen at 2D SIS, women with AUB are treated first with expectant management or hormonal therapy. Among postmenopausal women with uterine bleeding, the main focus of testing is to exclude endometrial cancer or precancer (atypical endometrial hyperplasia). Four types of diagnostic tests are used: sonographic measurement of endometrial thickness, endometrial sampling, hysteroscopy and SIS. Consensus regarding the sequence in which these methods should be employed in women with PMB is lacking (van Hanegem 2011). However, most guidelines recommend TVS as the first-line test, and that women with an endometrial thickness greater than 4 mm should undergo endometrial sampling. If histological diagnosis is inconclusive, or if PMB recurs, guidelines recommend that an outpatient hysteroscopy with concomitant endometrial biopsy should be planned (Guideline ACOG; Guideline NVOG; Guideline RCOG).

Rationale

Polyps and submucous fibroids are associated with AUB and subfertility. SIS is a minimally invasive, cost-efficient, outpatient test that can detect these focally growing lesions with a good degree of accuracy (Bij de Vaate 2010; de Kroon 2003) without the need for more invasive and costly hysteroscopy. Detected lesions can be removed subsequently in the hope of alleviating AUB symptoms, excluding malignant or premalignant disease (van Hanegem 2016) and optimising fertility (Bosteels 2015). A meta-analysis of the accuracy of 2D SIS (with hysteroscopy as the gold standard) in AUB revealed pooled sensitivity and specificity of 95% and 88%, respectively (de Kroon 2003). High sensitivity in 2D SIS means that additional diagnostic methods (such as diagnostic hysteroscopy) may be avoided if a normal uterine cavity is detected with SIS. However, 5% of uterine cavity abnormalities were missed and 12% of women without abnormalities were scheduled for unnecessary hysteroscopy as the result of a false-positive test result (they were found to have a normal uterine cavity).

Saline infusion sonography has been performed conventionally with 2D ultrasonic imaging. However, 2D SIS may not be fully accurate in assessment of the type and classification of intrauterine abnormalities (Kroon 2006). Three-dimensional SIS appears to enhance visualisation of the uterine cavity and may help discriminate between polyps and submucous fibroids. Furthermore, 3D SIS can very accurately measure the size and extent of protrusion of submucous fibroids into the uterine cavity (Lee 2006; Mavrelos 2011); these parameters are important determinants for the planning of hysteroscopic procedures in terms of the need for pharmaceutical endometrial downregulation, appropriate treatment setting, type of anaesthesia, choice of surgical instruments and required surgical expertise (Betjes 2009; Wamsteker 1993). Another benefit of an accurate imaging diagnosis is the potential to skip a surgical procedure and provide medical therapy (e.g. oral contraceptives, levonorgestrel-releasing intrauterine system). In the case of fibroids, medical therapy such as a gonadotropin-releasing hormone agonist or a selective progesterone receptor modulator can be considered before surgery (Lethaby 2002; Sancho 2016). Enhanced detection and classification of focally growing intracavitary lesions might result in improved patient outcomes as a result of better treatment and reduced morbidity from unnecessary hysteroscopies or missing abnormalities. Despite the high accuracy reported for 3D SIS in the diagnosis of uterine abnormalities, 2D SIS is usually used in clinical practice because consistent evidence of the diagnostic benefit of 3D imaging and availability of 3D ultrasonic probes are insufficient.

OBJECTIVES

Primary objectives

- To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS for the diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test**.**
- To evaluate the diagnostic accuracy of 2D+3D SIS (index test 2) compared with 2D SIS for the diagnosis of focally growing lesions (presence or not) in women with AUB or subfertility, with hysteroscopy performed as the reference test**.** In this case, any abnormality on either modality was regarded as a positive result ('OR' approach).

Secondary objectives

- To evaluate the diagnostic accuracy of 3D SIS (index test 1) compared with 2D SIS according to type of abnormality and discrimination between uterine polyps and submucous fibroids in women with AUB or subfertility, with hysteroscopy and histology used as the reference.

- To evaluate the diagnostic accuracy of 2D+3D SIS (index test 2) compared with 2D SIS according to type of abnormality and discrimination between uterine polyps and submucous fibroids in women with AUB or subfertility, with hysteroscopy and histology used as the reference.

METHODS

Criteria for considering studies for this review

Types of studies

All diagnostic test accuracy studies, randomised controlled trials and prospective cohort studies for which a 2×2 contingency table could be reproduced in which 2D SIS and 3D SIS were evaluated with results of hysteroscopy as the reference standard were eligible for inclusion in the review. All studies in which 2D SIS or 3D SIS alone was evaluated were considered eligible for inclusion, although if enough studies (10) were found, we preferred studies that reported both 2D SIS and 3D SIS. We included comparative studies if both 2D SIS and 3D SIS were performed in the same setting, regardless of performance sequence, to avoid a difference in performance between index tests arising from differences among participants and settings. We excluded case control, case report and retrospective cohort studies. We contacted the authors of unpublished studies (only congress abstract or published protocol was available) to facilitate inclusion of additional useful data. We did not apply language restrictions.

Participants

Populations of interest were premenopausal women with AUB or subfertility and postmenopausal women with AUB.

Index tests

We included studies comparing the diagnostic accuracy of 3D SIS alone (index test 1) or 2D+3D SIS (index test 2) versus 2D SIS (comparator test). We defined SIS as positive for a focal intrauterine lesion when any distortion of the endometrial lining was visualised (see below). We preferred that time between index test and reference standard was less than one month.

Target conditions

The target condition was the presence (or absence) of a focally growing lesion in the uterine cavity (endometrial polyp, submucous fibroid). We differentiated between polyps and fibroids by classifying smoothly margined echogenic masses with a

homogenous texture as polyps (Parsons 1993), and well-defined round lesions within the myometrium or attached to it, often showing shadows at the edge of the lesion and/or internal fan-shaped shadowing, as uterine fibroids (van den Bosch 2015a). Typically, echogenicity varies and some hyperechogenicity may be present internally. We classified submucous fibroids into types of fibroid (types 0 to 2) using the International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN classification for abnormal uterine bleeding: type 0 = pedunculated intracavitary, 1 = submucosal < 50% intramural, 2 = submucosal ≥ 50% intramural (Munro 2011). We did not consider hyperplasia, adhesions and congenital anomalies as focally growing lesions.

Reference standards

Diagnostic hysteroscopy was the reference standard for confirmation of the absence or presence of the target condition. Absence of an intracavitary abnormality was seen as clear vision of the entire cavity without disruption of the endometrial lining. When reported, we also used histology as a reference standard to differentiate the type of abnormality (polyp or fibroid). Because the sensitivity for 2D SIS is known to be high (de Kroon 2003), it might be considered unethical to perform hysteroscopy in women with a negative SIS test (meaning no suspicion of abnormality). To optimise data quantity, we included data from studies with partial verification bias (i.e. when some women did not undergo a hysteroscopy (reference standard) after a negative test result with 2D SIS).

Search methods for identification of studies

Electronic searches

We performed searches in consultation with the Cochrane Gynaecology and Fertility Group (CGFG) Information Specialist without language restrictions from inception until 1 March 2016.

We searched the following electronic databases.

- On the web: Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) (Appendix 1). We searched the trial registries of clinicaltrials.gov (Appendix 2) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (Appendix 3). We searched PubMed (Appendix 4) to find published trials not yet indexed in MEDLINE.
- Ovid: MEDLINE (Appendix 5) and Embase (Appendix 6) databases.
- ProCite, the CGFG Specialised Register for Randomised Controlled Trials (RCTs) (Appendix 7) and the CGFG Diagnostic Test Accuracy (DTA) Specialised Register (Appendix 8).

Searching other resources

We carried out a handsearch by screening the reference lists of all included articles. We screened available online conference abstracts in the field of gynaecology.

Data collection and analysis

Selection of studies

Two review authors (LLN and FJRH) independently read all potential studies after first screening by title and abstract (also performed independently by LLN and FJRH). We resolved disagreements on decisions for inclusion through discussion; when agreement was not reached, we consulted a third review author (HAMB). We considered all prospective studies comparing 2D SIS and 3D SIS with hysteroscopy as eligible. We used ENDNOTE as our bibliographic management system. We removed duplicates after checking each study by hand and verified all studies in multiple papers of the same study.

Data extraction and management

Two review authors (LLN and FJRH) independently extracted data from eligible studies - all written in English. We resolved disagreements by discussion between review authors; when agreement was not reached, we consulted a third review author. We contacted study investigators to request additional data on methods and results when we noted missing information or inconsistencies.

Assessment of methodological quality

Two review authors (LLN and FJRH) worked independently to assess studies for methodological quality using QUADAS-2 (revised tool for quality assessment of diagnostic accuracy studies) (Whiting 2011). The QUADAS-2 tool consists of four different domains: patient selection, index test, reference standard, flow and timing. Each domain comprises questions used to assess risk of bias and to address applicability concerns. We supplemented the QUADAS-2 tool with review-specific questions (Table 1). For example, in the index test domain, we added the question whether the level of experience of the (index) test performer was reported. We added to the reference test and target condition domain the question whether the target condition was specified and in which categories. To assess quality, we scored all four domains as having low, unclear or high risk of bias and low or high concern regarding applicability.

Statistical analysis and data synthesis

Data synthesis

The main objective of this review and meta-analysis was to assess the accuracy of (2D+)3D SIS compared with 2D SIS in detecting focally growing lesions. We expected to include studies that evaluated 2D SIS and 3D SIS against the reference standard, as well as studies that evaluated the combination of 2D SIS and 3D SIS against the reference standard. If we found fewer than 10 of these latter studies, we included studies that evaluated 2D SIS or 3D SIS alone.

For studies in which multiple index tests (2D SIS, 2D+3D SIS and 3D SIS) were performed, we constructed a series of 2×2 contingency tables that combined results of investigations provided that they were derived from the total study population and that the definition of a positive result was given for one of the tests.

A secondary objective was to assess the accuracy of index tests according to type of abnormality, while differentiating between polyps and fibroids. In this case, we used the same analyses as described below but the target condition was polyp (vs no polyp) or submucous fibroid (vs no submucous fibroid), depending on what was reported. We wanted to differentiate between polyps and fibroids but could not prepare a 2×2 table because several results were possible. Therefore, in the chosen analyses, we did not directly differentiate between polyps and fibroids but instead analysed them as polyp (vs no polyp) or submucous fibroid (vs no submucous fibroid).

Statistical analysis

To describe and visualise the data, we produced in RevMan forest plots showing pairs of sensitivity and specificity together with 95% confidence intervals from each study, as well as raw receiver operating characteristic (ROC) plots for 2D SIS and for 3D SIS. We displayed paired analyses (studies that tested both 2D SIS and 3D SIS) in an ROC plot by linking sensitivity-specificity pairs from each study with a dashed line (Leeflang 2008).

To compare 3D SIS versus 2D SIS, we restricted our analyses to studies that provided 2×2 tables for both tests, and we used the bivariate meta-analysis of sensitivity and specificity, while allowing for variation in variance of the logit sensitivity and specificity (Reitsma 2005). Even with few studies and/or sparse data (owing to 100% sensitivity or specificity), the advice is to use a hierarchical model (Takwoingi 2015). In cases of fewer than five studies, or when the models did not converge, we planned to use a univariate random-effects logistic regression model.

To analyse the addition of 3D SIS to 2D SIS, we included studies that reported accuracy for the combination of these two techniques. In this case, we regarded as a positive result any abnormality seen on either of the two modalities ('OR' approach). This means that both tests do not need to be positive, if either of the two tests (2D SIS or 3D SIS) was positive and the other negative we considered the test positive. If both tests were negative we considered the test negative.

For 3D SIS, we noted minimal variation in specificity and quite some variation in sensitivity. The models converged only if we assumed no correlation between logit sensitivity and logit specificity, probably because results showed very little heterogeneity, with almost all studies reporting specificity of 100%. If sensitivity varies and specificity does not, the assumption of no correlation may be valid.

We presented results as summary sensitivity and summary specificity. We used the graphical display of a false-positive (1 - specificity) versus a sensitivity plot (ROC plot) showing individual study results, including individual study estimates, the summary operating point (summary values for sensitivity and specificity) and the 95% confidence region on the operating point.

Investigations of heterogeneity

We addressed heterogeneity by adding variables to the bivariate model as covariates if both subgroups included at least three studies. We performed these analyses for clinical symptoms (bleeding vs subfertility); prior testing (prior testing or not); and whether evaluation of 2D or 3D SIS was blinded for clinical information. We also wanted to evaluate the effect of menopausal state (premenopausal or postmenopausal), but the models did not converge when we added this information as a covariate. We also assessed heterogeneity with forest plots and ROC plots.

Sensitivity analyses

We conducted sensitivity analyses to determine whether the methodological characteristics (as assessed by domains of the QUADAS-2 tool) of included studies influenced summary estimates of sensitivity and specificity. We evaluated what would have happened if we would have removed studies at high risk of bias for either of the QUADAS-2 domains. In case of missing or uninterpretable index tests (failure of 2D SIS or 3D SIS), data were classified as positive test results.

Assessment of reporting bias

We aimed to minimise potential impact by ensuring a comprehensive search for eligible studies and by staying alert for duplication of data. We applied no language restrictions and required no translations. We contacted the authors of unpublished studies to ask for data and full text; unfortunately, this information was not available. We recorded ongoing studies.

RESULTS

Results of the search

In total, we identified 7335 studies. After removing duplicates, two review authors (LLN and FJRH) independently screened 5242 studies by title. We carried out a handsearch by screening the reference lists of all included articles as well as available online conference abstracts in the field of gynaecology; this yielded no additional studies. Of the 5242 studies screened by title, we found that 1017 required screening by abstract. Both review authors independently screened 1017 abstracts. Subsequently, both review authors assessed 46 full-text articles for eligibility. We resolved disagreements through short discussion. For two studies, we consulted a third review author (HAMB) and reached agreement.

We found more than 10 studies reporting 3D SIS (compared with 2D SIS) and included all of them in the review. Because the accuracy of 3D SIS is our main question and we found enough studies, we did not include studies reporting only 2D SIS (21 studies). We excluded another 12 studies because 2×2 tables could not be constructed or because investigators used a different index test or reference test; five of those 12 studies (Abou-Salem 2010; Ahmad 2014; Khan 2011; Makris 2005; Makris 2007a) did not use hysteroscopy (but used histology) as the reference standard. Ayida 1996 compared 2D and 3D SIS in five participants without using a reference standard. Ayoubi 2002 reported about software used to create a virtual hysteroscopy, which investigators tested in five participants. Jurisic 2013 used a different index test - 3D multi-slice - and for Ahmadi 2013 and Lagana 2014, it was impossible to build a 2×2 table.

We included the remaining 13 studies for qualitative synthesis. Two of 13 studies (Kowalczyk 2012; Nieuwenhuis 2014) reported accuracy only for type of abnormality (secondary objective). We were able to include the other 11 studies in a meta-analysis. For details of the screening and selection process, see Figure 1. We did not find multiple papers of the same study. Included studies were published and performed between

1999 and 2015 in the following countries: Italy, Greece, England, Poland, the Netherlands, Egypt and Canada. None of these studies reported conflicts of interest. We found two ongoing studies (see Characteristics of ongoing studies).

Methodological quality of included studies

The main problem involving the quality of included studies is insufficient reporting of study methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, we considered the overall quality of the evidence as low.

Of the 13 included studies, 12 were prospective observational cohort studies and one was an RCT (Katsetos 2013). We found that methodological quality was often difficult to assess, as researchers did not clearly report the required information. We contacted study authors because we found conflicting results presented in the text and tables (leading to inability to complete 2×2 tables). Responses were not always helpful, but in all cases, we were able to prepare 2×2 tables.

Figure 2 and Figure 3 show bias and applicability for all included studies for each domain as scored by QUADAS-2. Some empty spaces are apparent in Figure 3, all for the index test 2D SIS. In these cases, investigators reported only 3D SIS, so quality assessment for 2D SIS was not applicable.

For all studies, we had few applicability concerns. Figure 2 demonstrates that for all domains, half of the studies showed low risk of bias. We have addressed risk of bias for each domain separately below. The Characteristics of included studies section presents details of each domain separately for every study (Aboulghar 2011; Adel 2014; de Kroon 2004; El-Sherbiny 2011; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; Kupesic 2007; La Torre 1999; Makris 2007; Nieuwenhuis 2014; Sconfienza 2010; Sylvestre 2003).

- *Patient selection domain:* Six studies showed low risk of bias (de Kroon 2004; Katsetos 2013; Kowalczyk 2012; Kupesic 2007; Nieuwenhuis 2014; Sylvestre 2003), and the other seven showed unclear risk. Seven studies included participants with abnormal uterine bleeding (Adel 2014; de Kroon 2004; Katsetos 2013; Kowalczyk 2012; Makris 2007; Sconfienza 2010; Sylvestre 2003), three included participants with subfertility (Aboulghar 2011; El-Sherbiny 2011; Kupesic 2007) and three included both groups (El-Sherbiny 2015; La Torre 1999; Nieuwenhuis 2014). Seven studies did not state consecutive inclusion but did report the inclusion period. It remains unclear if included patients represented a random sample (unclear risk of bias). Six of 13 studies did not report a prior test (Adel 2014; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; Kupesic 2007; Sconfienza 2010). It is unclear whether

these participants received 2D SIS and 3D SIS directly and 2D ultrasonography was passed over (uncommon in clinical practice). Therefore, risk of bias is unclear but cannot be considered high because included patients were clinically suspected of having intracavitary abnormalities. One study (El-Sherbiny 2011) included only patients with a negative prior test (normal 2D ultrasonography) and did not report patients with an abnormal prior test; therefore, we considered selection bias as unclear.

- *Index test domain:* All 13 studies reported 3D SIS (index test 1), 10 also reported 2D SIS (comparator test) and three had not studied 2D SIS (Adel 2014; Katsetos 2013; Makris 2007). Investigators performed all index tests for 2D SIS and 3D SIS in the same way across included studies and presented the same well-reported criteria for presence or absence of the target condition (a threshold was not applicable in all studies). We judged seven studies (Aboulghar 2011; Adel 2014; de Kroon 2004; Kowalczyk 2012; La Torre 1999; Sconfienza 2010; Sylvestre 2003) as having unclear risk of bias owing to unclear blinding. It was unclear whether index tests were interpreted without knowledge of the reference standard. We considered the others to have low risk of bias (n = 6).
- *Reference standard domain:* All studies used a reference standard (hysteroscopy) that was likely to correctly classify the condition. In five of 13 studies (Aboulghar 2011; Adel 2014; Kowalczyk 2012; La Torre 1999; Sconfienza 2010), it was unclear whether hysteroscopy was interpreted without knowledge of the index tests. One study (de Kroon 2004) did not blind observers to index test results; therefore, we judged this study to have high risk of bias.
- *Flow and timing domain:* We found most concerns regarding bias in this domain. We judged seven studies as having low risk of bias (Aboulghar 2011; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; Kupesic 2007; La Torre 1999; Makris 2007) and the other six as having unclear (Adel 2014; El-Sherbiny 2011; Sconfienza 2010) and high risk (de Kroon 2004; Nieuwenhuis 2014; Sylvestre 2003). We based this classification on several concerns. Six studies did not report failures and/or complications and did not always make clear whether all patients were included in the study and in the final analyses. Seven studies reported an unclear time interval between SIS and hysteroscopy (Aboulghar 2011; Adel 2014; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; La Torre 1999; Sylvestre 2003). Three studies did not always use the reference standard, resulting in high risk of verification bias. Most studies did not report experience in performing and interpreting index tests and reference standard results.

Twelve of 13 studies were observational cohort studies. Observational studies are the next best method after RCTs in terms of quality of evidence, according to the GRADE Working Group (Guyatt). Study design for diagnostic test studies is challenging. To address test accuracy, we can consider observational studies with a good design and performed in a proper manner according to the STARD checklist (Cohen 2015) as having higher quality. Although the design of included studies seems applicable, the main problem involving the quality of included studies is insufficient reporting of study methods, resulting in unclear risk of bias for the several QUADAS-2 domains. Therefore, we rated the quality of the evidence as low.

Findings

We found 13 studies that evaluated 3D SIS with hysteroscopy as a reference standard (Aboulghar 2011; Adel 2014; de Kroon 2004; El-Sherbiny 2011; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; Kupesic 2007; La Torre 1999; Makris 2007; Nieuwenhuis 2014; Sconfienza 2010; Sylvestre 2003); 10 of these also reported 2D SIS (Aboulghar 2011; de Kroon 2004; El-Sherbiny 2011; El-Sherbiny 2015; Kowalczyk 2012; Kupesic 2007; La Torre 1999; Nieuwenhuis 2014; Sconfienza 2010; Sylvestre 2003).

All 13 studies (1053 women) reported accuracy for 3D SIS, and 11 of these (846 women) reported accuracy in detecting the presence/absence of any abnormality (Aboulghar 2011; Adel 2014; de Kroon 2004; El-Sherbiny 2011; El-Sherbiny 2015; Katsetos 2013; Kupesic 2007; La Torre 1999; Makris 2007; Sconfienza 2010; Sylvestre 2003). Eight studies (Aboulghar 2011; Adel 2014; El-Sherbiny 2011; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; La Torre 1999; Nieuwenhuis 2014) reported the presence/absence of a specific abnormality (polyp or fibroid). Study size ranged from 23 to 180 participants. Prevalence of the target condition ranged from 14% to 96%.

Primary objectives

The accuracy of 3D SIS was based on the reporting accuracy of 11 studies in detecting intracavitary abnormalities (presence/absence), which we used for quantitative analyses. Summary estimates for sensitivity and specificity were 94.5% (95% confidence interval (CI) 90.6% to 96.9%) and 99.4% (95% CI 96.2% to 99.9%), respectively, evaluated against hysteroscopy.

Diagnostic accuracy of 3D SIS (index test 1) in comparison with 2D SIS

Meta-analysis of the eight studies (N = 716) directly comparing 2D SIS and 3D SIS (index test 1) (Aboulghar 2011; de Kroon 2004; El-Sherbiny 2011; El-Sherbiny 2015; Kupesic 2007; La Torre 1999; Sconfienza 2010; Sylvestre 2003) showed that both sensitivity and

specificity are higher for 3D SIS than for 2D SIS (see Figure 4 for forest plot, Figure 5 and Figure 6 for summary receiver operator characteristics (SROC) plots), although this difference was not statistically significant (P values of 0.07 for sensitivity and 0.10 for specificity). Figure 5 shows a SROC plot for both 2D SIS and 3D SIS. Figure 6 additionally shows sensitivity-specificity pairs from studies that studied both 2D SIS and 3D SIS; these are linked with a dashed line. Results for 2D SIS showed greater variation in specificity than those for 3D SIS. Mean sensitivity of 3D SIS was approximately the same as in the complete set of 11 3D SIS studies: sensitivity 96.9% (95% CI 91.9% to 98.8%); specificity 99.5% (95% CI 96.1% to 100%). Mean sensitivity for 2D SIS was 90.9% (95% CI 81.2% to 95.8%) and for specificity 96.3% (95% CI 86.1% to 99.1%). Inspection of the forest plots reveals that sensitivity and specificity for 3D SIS were similar among studies.

Diagnostic accuracy of 2D SIS+3D SIS (index test 2) in comparison with 2D SIS

We found only one study (Nieuwenhuis 2014) that compared 2D SIS and 3D SIS together versus 2D SIS with hysteroscopy as a reference. Investigators did not report accuracy for the presence or absence of an abnormality but did report accuracy for detection of uterine polyps and submucous fibroids. We found only one study that used index test 2; therefore, additional (meta-)analyses were not possible.

To characterise the usefulness of the test in different prevalence scenarios, we calculated post-test probabilities (PPVs) for three different values of prevalence: 15%, 50% and 90%. PPV would be 96.0%, 99.3% and 99.9%, respectively.

Secondary objectives

Diagnostic accuracy of 3D SIS in comparison with 2D SIS for type of abnormality: polyp or submucous fibroid

Polyps

Eight studies (Aboulghar 2011; Adel 2014; El-Sherbiny 2011; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; La Torre 1999; Nieuwenhuis 2014), with a total of 690 women, reported accuracy of 3D SIS in detecting polyps, and their summary sensitivity and specificity values were 96.3% (95% CI 79.4% to 99.4%) and 99.9% (95% CI 93.8% to 100%), respectively. This was comparable with the overall sensitivity for 3D SIS. Six studies reported accuracy for 2D SIS in detecting polyps; however, the models did not converge for this subgroup. Therefore, a formal comparison could not be made. However, five of six studies found that 3D SIS was more sensitive (improved approximately from 80% to 100%) and equally specific; one study found that 3D SIS was more specific and equally sensitive (Figure 7).

Fibroids

Six studies (Adel 2014; El-Sherbiny 2011; El-Sherbiny 2015; Katsetos 2013; Kowalczyk 2012; Nieuwenhuis 2014), with a total of 599 women, reported accuracy of 3D SIS in detecting fibroids, and four studies reported accuracy of 2D SIS in detecting fibroids (Figure 7). Inspection of the forest plot reveals that in three of four studies, 3D SIS was more sensitive (60% to 90% to 75% to 100%) and equally specific. In the fourth study, 3D SIS was equally sensitive (95%) and less specific (94% to 90%). It is unclear if the higher sensitivity for 3D SIS is a result of more accurate measurement of protrusion with 3D SIS. Study authors did not report percentage of protrusion for 2D SIS nor for 3D SIS.

Diagnostic accuracy of 2D SIS+3D SIS in comparison with 2D SIS for type of abnormality: polyp or submucous fibroid

For detecting polyps, Nieuwenhuis 2014 reported that sensitivity and specificity improved from 83% and 87% for 2D SIS to 89% and 89% for 2D SIS+3D SIS.

For detecting fibroids, sensitivity improved with no effect on specificity: from 95% and 94% for 2D SIS to 98% and 94% for 2D SIS+3D SIS.

Sensitivity analyses

Original summary estimates for 3D SIS sensitivity and specificity were 94.5% and 99.4%, respectively. We found no missing or uninterpretable data. One study (de Kroon 2004) had high risk of bias for the reference standard. When we removed this study, summary sensitivity for 3D SIS was 94.6% (95% CI 90.3% to 97.1%) and summary specificity was 99.4% (95% CI 96.0% to 99.9%). Two of eight studies suffered from partial verification bias (de Kroon 2004; Sylvestre 2003). We were unable to perform sensitivity analyses on these two studies, as not enough data remained when they were removed. These were the oldest studies, and the forest plot shows that they had the highest estimates of sensitivity and the lowest estimates of specificity for 2D SIS. Removing them from the analyses might have lowered sensitivity and raised specificity values for 2D SIS. Three-dimensional SIS results were more uniform across different studies. Several studies had unclear risk of bias for patient selection and study sample. One of those studies (El-Sherbiny 2011) included patients with a normal cavity on 2D ultrasonography, which is different from all other studies in that investigators included patients with (complaints and) an abnormal 2D ultrasound. When we removed this study from the set, summary sensitivity for 3D SIS was 94.9% (95% CI 90.4% to 97.3%) and summary specificity was 99.1% (95% CI 95.2% to 99.8%).

DISCUSSION

Summary of main results

Thirteen studies (1053 women) reported accuracy of three-dimensional saline infusion sonography (3D SIS) and met the inclusion criteria. Summary estimates for sensitivity and specificity were 94.5% and 99.4%, respectively, evaluated against hysteroscopy. Meta-analysis (of eight studies) comparing two-dimensional (2D) SIS and 3D SIS showed no statistically significant differences (P values of 0.07 for sensitivity and 0.10 for specificity) in detecting intracavitary lesions with hysteroscopy as a reference standard. Mean sensitivity and mean specificity were higher for 3D SIS (96.9% and 99.5%) than for 2D SIS (90.9% and 96.3%). Detection of specific abnormalities (endometrial polyps and submucous fibroids) in most studies showed higher sensitivity for 3D SIS. Only one study reported on 2D SIS+3D SIS versus 2D SIS and found improved sensitivity (with equal or improved specificity). The design of included studies seems applicable. The main problem involving the quality of included studies is insufficient reporting of study methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, we considered the overall quality of the evidence as low. Sensitivity analyses performed showed little effect on the data. We have provided a review summary in Summary of findings table 1.

Strengths and weaknesses of the review

This is the first review conducted to study the accuracy of 3D SIS in detecting an intracavitary abnormality with hysteroscopy as a reference standard. We studied differences between 2D SIS and 3D SIS in meta-analysis and carried out subgroup analyses for polyps and fibroids. We conducted this review as published in the protocol and have reported minor differences below. We contacted the authors of potential studies for inclusion when important information was unclear, when only an abstract was available or when 2×2 tables could not be reconstructed. We kept to our strict inclusion criteria and included only studies in which a 2×2 table for 3D SIS (and 2D SIS) could be constructed. Another strength of the review is that we compared 2D SIS versus 3D SIS using only studies that reported both index tests. These within-study comparisons reporting both 2D SIS and 3D SIS provide results of comparisons of the same index tests and reference standard used in the same population. Differences in performance between index tests are not explained logically by different patients and settings. We analysed studies reporting only polyps or fibroids separately in the same manner.

However, this review has some limitations. In selecting studies, we chose to exclude studies in which pathology was the (only) reference standard. Studies using pathology as a reference focused on the origin of the abnormality (endometrium or myometrium) such that they included endometrial hyperplasia, which is usually seen as a diffuse endometrial lesion - not as a focal abnormality. In this review, we focused on the presence of an acquired, focal abnormality - not on the origin of the abnormality. We excluded studies reporting on uterine anomalies in general (not differentiating between global and focal intracavitary or congenital and acquired abnormalities) to keep groups of participants homogeneous. Lack of information on intrauterine hyperplasia and intrauterine adhesions limits the applicability of this review with respect to these populations because we can report only the accuracy of 3D SIS in detecting focal abnormalities.

For our secondary objective, we wanted to differentiate between polyps and fibroids. In the chosen analyses, we do not directly differentiate between polyps and fibroids but analyse polyp yes or no and fibroid yes or no. In an ideal situation, we wanted to directly differentiate between them, but we could not prepare a 2×2 table because several results are possible. Current sensitivity and specificity values for polyp yes or no and fibroid yes or no indicate how well we recognise that particular abnormality. When we prepared the protocol, we had hoped to find studies that used a second index test: comparison of combined results of 2D SIS and 3D SIS versus results of a comparator test (2D SIS). We found only one study; therefore we could perform no further analyses. These questions might be answered in the future.

We tried to contact all study authors to clarify various items on applied methods, but despite these efforts, a large number of QUADAS-2 (revised tool for quality assessment of diagnostic accuracy studies) items that needed to be answered to estimate methodological quality remain unclear. For example, several studies did not report failures and complications. This is notable in a consecutive patient sample (> 50 to 200 participants) for both SIS and hysteroscopy procedures. This information may show how successful SIS and hysteroscopy are, or it might suggest that missing data were not always reported, and that this could have influenced accuracy. If results from 2D SIS or 3D SIS are unclear, they should not be excluded from analyses but should be reported as positive. If no complications or failures are reported, one might think it is unclear whether all participants were included in the final analysis. This could have had a major impact on results, seen mainly as an overestimation of accuracy for 2D SIS and 3D SIS. Another limitation of this review was the uncertainty of prior testing that could affect

prevalence. On the other hand, prevalence is spread from 14% to 96% among included studies, and results are comparable; effects on study results might be considered minimal.

This review included a broad spectrum of patients and methodological differences that resulted in a heterogeneous group, impeding meta-analysis. For example, the broad spectrum resulted in a wide range of prevalence of the target condition. High prevalence suggests a highly selected patient population and can be seen as a weakness, although in clinical practice, it is not surprising that women with abnormal uterine bleeding (AUB) and a positive prior test will have a positive result at index testing. Even with this wide range of underlying disease prevalence, accuracy results remained similar for all studies.

Applicability of findings to the review question

All studies showed applicable patient selection and study design (at quality assessment using QUADAS-2), thus answering the question of diagnostic test accuracy. Findings of sensitivity and specificity observed between studies showed comparable results in terms of accuracy. Large variation is evident in prevalence of the target condition between studies. We included in the review both women with abnormal bleeding (premenopausal and postmenopausal) and women with subfertility. Prevalence was lowest in subfertile women and highest among women with AUB, as expected in clinical practice.

The time interval between SIS and hysteroscopy was unclear in some studies. This could have affected diagnosis or verification of the target condition. In clinical practice, these procedures follow each other quickly owing to availability, patient complaints and probability of diagnosis. It is not likely that time between procedures would be long enough for the target condition to change substantially. Another flaw that we found was unclear blinding of index results for the performer of the hysteroscopy (reference standard). Knowledge of the index test result could affect judgement of hysteroscopy findings, resulting in different assessment of test accuracy. In clinical practice, the physician performing hysteroscopy will usually know the findings of ultrasonography or SIS. During hysteroscopy, the shape, colour and texture of the cavity, endometrium and abnormality can be seen more clearly. Most likely, ultrasound findings have not affected the results of hysteroscopy because hysteroscopy probably overrules these findings. Therefore, we reported risk of bias as unclear or high, but we expect the effect on study results to be minimal.

A potential risk of verification bias results from the fact that the reference standard was not always performed when SIS was normal, leading patients to receive hysteroscopy only when SIS was abnormal. This may have influenced sensitivity and specificity. We do not know how this may have influenced these parameters, but we do know that El-Sherbiny 2011, which included only patients with a negative SIS, had comparable results for sensitivity and specificity.

Some studies did not report experience in performing and interpreting index tests. As 3D SIS is not a common practice in every hospital, it is likely that the procedure was performed by experts. Therefore, reported accuracy may be lower in everyday practice. As 2D SIS was probably also performed by experts, improved accuracy cannot be explained by the performer's experience. Mainly as a result of this poor reporting of methods in the included studies, we classified these uncertainties as having 'unclear risk of bias' in quality assessment based on QUADAS-2. It is possible that poor reporting/ unclear risk of bias may have little effect on the results, but included studies should have reported the missing information. Therefore, we considered the overall quality of the evidence to be low. All studies proved to be applicable at quality assessment and can be considered representative for answering the main review question.

AUTHORS' CONCLUSIONS

Implications for practice

Low-quality evidence showed that 3D SIS is highly accurate in detecting intracavitary abnormalities. Meta-analysis revealed no statistically significant differences between 2D SIS and 3D SIS. Summary sensitivity and specificity are higher for 3D SIS, but margins of improvement are limited in that 2D SIS is already very accurate. 3D SIS is an alternative to 2D SIS when the technology and appropriate expertise are available. Both 2D SIS and 3D SIS should be considered alternatives to diagnostic hysteroscopy when intracavitary pathology is suspected in both subfertile women and those with abnormal uterine bleeding.

Implications for research

2D SIS and 3D SIS are frequently studied for detection of intracavitary abnormalities. Still, the sample size of studies in our meta-analysis might have been too small to show a difference. As the P value is close to 0.05, it would be interesting if more studies were conducted to determine whether a difference exists between 2D SIS and 3D SIS

for detection of acquired focal uterine abnormalities. In addition, the low quality of evidence might suggest that solid methodological research must confirm previous findings.

It is unknown whether purchased materials (3D probe, software, etc.) and the learning curve outweigh any potential diagnostic advantage associated with 3D ultrasonic imaging. It is also unknown how effective 3D SIS is when 2D SIS is inconclusive. Future studies must evaluate these benefits and costs. Only if 3D SIS is found to be accurate and effective in everyday practice should widespread implementation and training be recommended. A well-powered randomised controlled trial comparing these tests in clinical practice and performing a cost-effectiveness analysis would be a good first step.

Finally, we were able to include in this review only four studies reporting both 2D SIS and 3D SIS for fibroids, even though this review focused on detection of abnormalities rather than on indications for each type of treatment. It would have been interesting to learn more about the accuracy of protrusion measurement. Current treatment of submucous fibroids is provided via operative hysteroscopy, but with upcoming alternative radiological interventions such as ultrasonically guided ablation, this additional morphological information may be crucial. Thus, future studies should focus on the classification of submucous fibroids.

ACKNOWLEDGEMENTS

We would like to thank the DTA Working Group and the Cochrane Gynaecology and Fertility Group for their specialist peer review comments. We thank Marian Showell (Information Specialist) for her great help with the search strategy. We thank Helen Nagels for her help and overall advice.

Contributions of authors

- LL Nieuwenhuis: conceiving of the review, coordinating the review, providing a clinical perspective, designing search strategies, providing a methodological perspective, writing the review.
- FJR Hermans: providing a methodological perspective, writing the protocol.
- AJM Bij de Vaate: conceiving of the protocol, providing general advice on the protocol.
- MMG Leeflang: providing a methodological perspective, providing general advice on the review.
- HAM Brölmann: providing a clinical perspective, providing a policy perspective, providing a consumer perspective, providing general advice on the review, performing previous work that was the foundation of the current review.
- WJK Hehenkamp: providing a clinical perspective, providing a policy perspective, providing a consumer perspective, providing general advice on the review, performing previous work that was the foundation of the current review.
- BWJ Mol: providing a clinical perspective, providing a policy perspective, providing a consumer perspective, providing general advice on the review, performing previous work that was the foundation of the current review.
- TJ Clark: providing a clinical perspective, providing a policy perspective, providing a consumer perspective, providing general advice on the review, performing previous work that was the foundation of the current review.
- JAF Huirne: conceiving of the review, providing a clinical perspective, providing a policy perspective, providing a consumer perspective, providing general advice on the review, performing previous work that was the foundation of the current review.

Declarations of interest

The review authors have no conflicts of interest and no financial ties to disclose.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Primary objectives

Review: The primary objective of this review was to evaluate the diagnostic accuracy of 3D SIS (index test 1) in comparison with 2D SIS in the diagnosis of *focally growing lesions (presence or not)* in women with AUB or subfertility with hysteroscopy used as the reference test.
Protocol: focally growing lesions (polyps or fibroids).
In the protocol, the term 'polyps' or 'fibroids' is used to explain what is meant by focally growing lesions. It might be confusing because in the secondary objective, we differentiate between them. To make the primary objective more clear, we chose presence or not.

Types of studies

We state the following: All diagnostic test accuracy studies, randomised controlled trials and prospective cohort studies for which a 2×2 contingency table could be reproduced in which 2D SIS and 3D SIS were evaluated with results of hysteroscopy as the reference standard were eligible for inclusion in the review.
Review: 2×2 contingency table could be reproduced.
Protocol: sufficient methodological quality.
As inclusion based on "sufficient methodological quality" turned out to be difficult to objectively assess, we included only studies for which a 2×2 table could be reproduced.
Review: Prospective cohort studies will be included.
Protocol: Prospective cohort studies will be included if enrolment was performed consecutively.
As enrolment is a QUADAS-2 item, we removed 'consecutively' as this is not an exclusion criterion.
Review: Second, all studies in which 2D SIS or 3D SIS alone was evaluated were considered eligible for inclusion, although if enough studies (10) were found, we preferred studies that reported both 2D SIS and 3D SIS.
Protocol: In the protocol, we stated only 'enough' studies. In the review, we specified this as 10 studies.
Review: added the following: 'Authors of unpublished studies (only congress abstract or published protocol available) were contacted to facilitate inclusion of additional useful data. Language restrictions were not applied'.
Protocol: did not provide above information. As this information is important for the search, we added it to the review.

Index tests

Review: added the following: 'SIS was defined as positive for a focal intrauterine lesion when any distortion of the endometrial lining was visualised (see below). Time between index test and reference standard should preferably be less than one month'.
Protocol: A positive test result was not yet defined; therefore, we added this to the review. Second, a time interval was not yet described.

Target condition

The review extended ultrasonographic features of (submucous) fibroids with a more recent and widely supported reference. We also added information about classification of submucous fibroids.
Review: Smoothly margined echogenic masses with a homogenous texture were classified as polyps (Parsons 1993), and a uterine fibroid was seen as a well-defined round lesion within the myometrium or attached to it, often showing shadows at the edge of the lesion and/or internal fan-shaped shadowing (van den Bosch). Typically, echogenicity varies and some hyperechogenicity may be present internally. Submucous fibroids were classified into fibroid types (types 0 to 2) using the FIGO PALM-COEIN classification for abnormal uterine bleeding: type 0 = pedunculated intracavitary, 1 = submucosal < 50% intramural, 2 = submucosal ≥ 50% intramural (Munro 2011). Hyperplasia, adhesions and congenital anomalies were not considered as focally growing lesions.
Protocol: Smoothly margined echogenic masses with a homogenous texture are classified as polyps, and structures of mixed echogenicity disrupting endometrial continuity are described as submucous fibroids.

Reference standards

Review: added the following: 'The absence of an intracavitary abnormality was the clear vision of the entire cavity without any disruption of the endometrial lining'.

Protocol: Above information was lacking in the protocol and therefore was added to the review.

Electronic searches

Review: Performed search was presented in a more structured way.
Review: 'from inception till March 1, 2016'.
Protocol: 'from inception until present'.

Search of other resources

Review: Handsearch was carried out by screening the reference lists of all included articles.

Protocol: We will handsearch the reference lists of all included articles and will *contact experts in the field to obtain additional data*.
We did not contact any experts in the field other than listed coauthors and authors of included and (some) excluded studies.

Selection of studies

Review: added the following: 'ENDNOTE was used as a bibliographic management system. Duplicates were removed after each study was checked by hand. All studies were verified on multiple papers of the same study'.
Protocol: Above information was lacking in the protocol and therefore was added to the review.

Assessment of methodological quality

Review: added the following: 'The QUADAS-2 tool consists of four different domains: patient selection, index test, reference standard, flow and timing. Each domain includes questions used to assess risk of bias and to address applicability concerns'. 'To assess quality, all four domains were scored low, unclear or high risk of bias and low or high concern regarding applicability'.

Protocol: Above information was lacking in the protocol; to provide more information, we added the sentences above to the review.

Statistical analysis and data synthesis

Review: added the following: 'We wanted to differentiate between polyps and fibroids but a 2×2 table could not be prepared because several results were possible. Therefore, in the chosen analyses, we do not directly differentiate between polyps and fibroids but analyse them as polyp (vs no polyp) or submucous fibroid (vs no fibroid)'.
Analyses are the same in the protocol and in the review. In the review, we wanted to explain more clearly why we chose these analyses because we do not directly differentiate.
Review: added the following: 'Even with a low number of studies and/or sparse data (due to 100% sensitivity or specificity), the advice is still to use a hierarchical model (Takwoingi 2015). In case of fewer than five studies or if the models did not converge, we planned to use a univariate random-effects logistic regression model'.
We added information to the review to inform the reader about our decision to use a hierarchical model.
Review: added the following: 'For 3D SIS, we noted minimal variation in specificity and quite some variation in sensitivity. The models converged only if we assumed no correlation between logit sensitivity and logit specificity. This probably occurred

because very little heterogeneity was evident, with almost all studies reporting specificity of 100%. If sensitivity varies and specificity does not, the assumption that there is no correlation may be valid'.
As advice indicates that a hierarchical model should be used, we had to assume no correlation between logit sensitivity and logit specificity; we added this information to the review.
Protocol: Results will be presented as summary sensitivity and specificity, and additionally as likelihood ratios.
Review: Likelihood ratios were not reported.
As we had several objectives, and as results were well presented with summary sensitivity and specificity, we decided that presenting results in likelihood ratios as well would not provide additional value and would have resulted in too much information to report.

Investigations of heterogeneity

Review: added the following: 'prior testing (prior testing or not) and whether evaluation of 2D or 3D SIS was blinded for clinical information'.
We preferred to additionally evaluate the effects of these variables and therefore have added them to the review.
As heterogeneity can also be assessed with forest plots and ROC plots, we added this information to the section.

Sensitivity analyses

Protocol: We will conduct sensitivity analyses to determine whether conclusions are robust to arbitrary decisions made regarding eligibility of studies and analyses performed.
Review: In this review, we explained how we performed planned sensitivity analyses: 'We evaluated what would have happened if we would have removed studies with a high risk of bias for either one of the QUADAS-2 domains'. Second, we performed a sensitivity analysis for the effect of the reference standard.
Protocol: Missing or uninterpretable data were classified as positive test results.
Review: In this review, we clarified 'data' and changed the sentence: In case of missing or uninterpretable index tests (failure of 2D SIS or 3D SIS), data were classified as positive test results.
Protocol: 'We also performed a sensitivity analysis for the effect of the reference standard'.
Review: We removed the sentence above because the reference standard is one of the QUADAS domains, and we (already) stated the following; 'We evaluated what would have happened if we would have removed studies with a high risk of bias for either

one of the QUADAS-2 domains'. Studies with partial verification bias in the reference standard domain (not all women received the reference standard) were removed as part of sensitivity analyses to evaluate their influence on the main outcome.

FIGURES

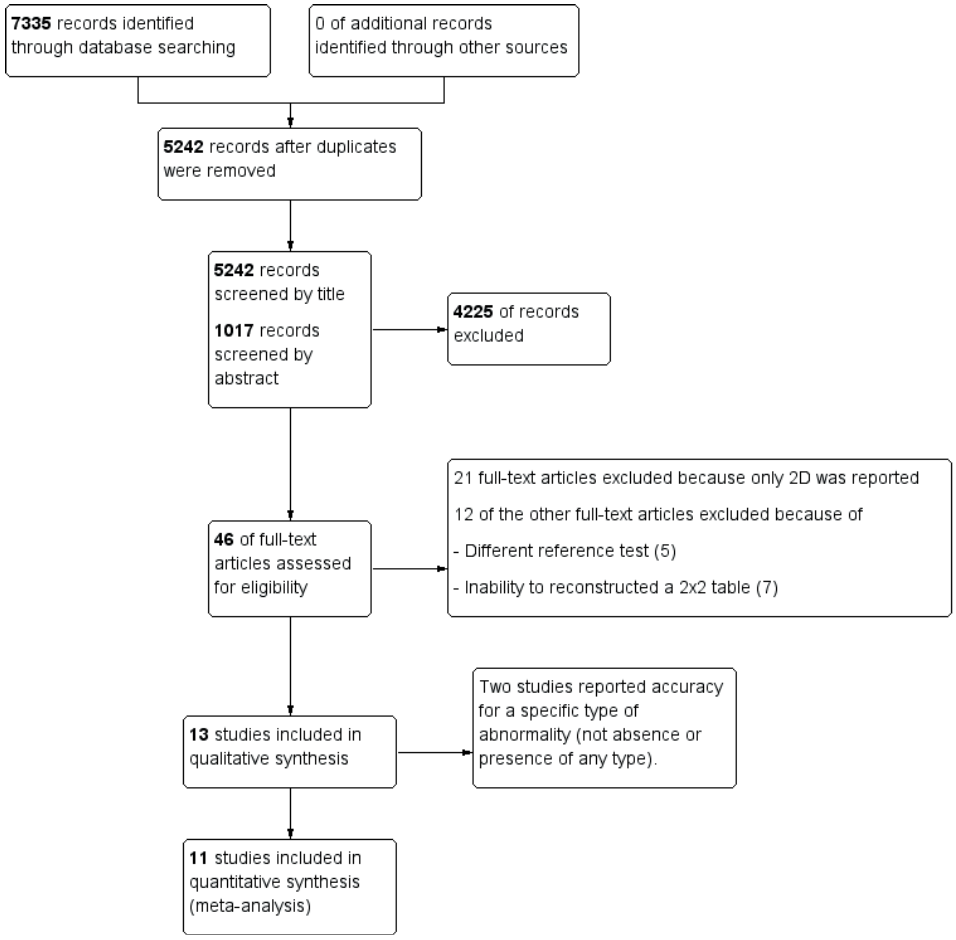


Figure 1. Study flow diagram.

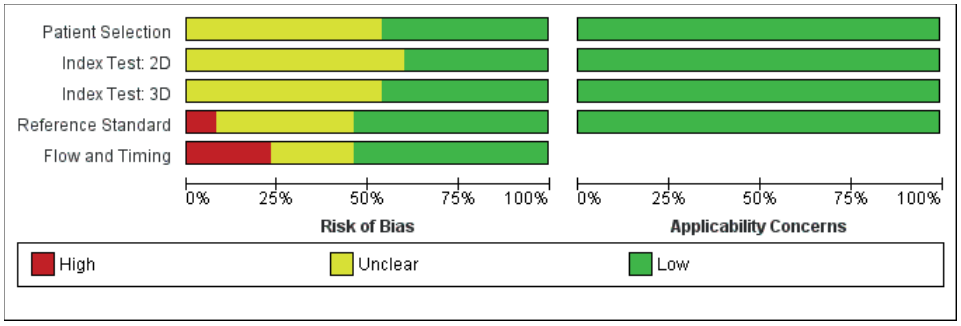


Figure 2. Risk of bias and applicability concerns graph: review authors' judgements about each QUADAS-2 domain presented as percentages across included studies.

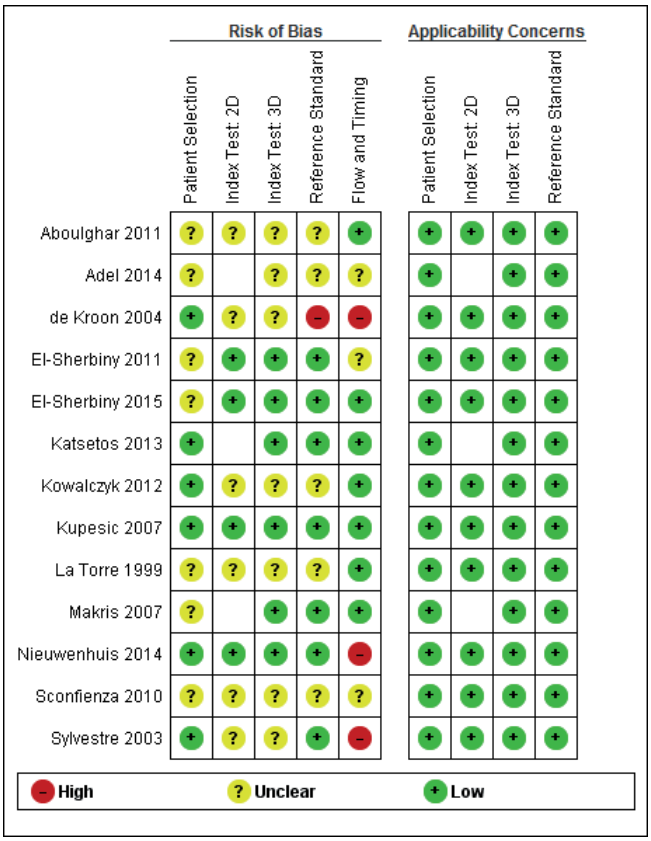


Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each QUADAS-2 domain for each included study.

2D SIS

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
La Torre 1999	20	1	0	2	1.00 [0.83, 1.00]	0.67 [0.09, 0.99]
Sylvestre 2003	76	4	2	11	0.97 [0.91, 1.00]	0.73 [0.45, 0.92]
de Kroon 2004	19	3	1	22	0.95 [0.75, 1.00]	0.88 [0.69, 0.97]
Kupesic 2007	44	1	3	104	0.94 [0.82, 0.99]	0.99 [0.95, 1.00]
Sconfienza 2010	19	0	2	3	0.90 [0.70, 0.99]	1.00 [0.29, 1.00]
Aboulghar 2011	44	0	7	27	0.86 [0.74, 0.94]	1.00 [0.87, 1.00]
El-Sherbiny 2011	19	0	8	154	0.70 [0.50, 0.86]	1.00 [0.98, 1.00]
El-Sherbiny 2015	37	4	15	64	0.71 [0.57, 0.83]	0.94 [0.86, 0.98]

3D SIS

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
La Torre 1999	20	0	0	3	1.00 [0.83, 1.00]	1.00 [0.29, 1.00]
Sylvestre 2003	42	4	0	47	1.00 [0.92, 1.00]	0.92 [0.81, 0.98]
de Kroon 2004	19	0	1	25	0.95 [0.75, 1.00]	1.00 [0.86, 1.00]
Kupesic 2007	47	0	1	67	0.98 [0.89, 1.00]	1.00 [0.95, 1.00]
Makris 2007	34	1	3	83	0.92 [0.78, 0.98]	0.99 [0.94, 1.00]
Sconfienza 2010	21	0	0	3	1.00 [0.84, 1.00]	1.00 [0.29, 1.00]
Aboulghar 2011	45	0	6	27	0.88 [0.76, 0.96]	1.00 [0.87, 1.00]
El-Sherbiny 2011	25	0	2	106	0.93 [0.76, 0.99]	1.00 [0.97, 1.00]
Katsetos 2013	22	0	4	18	0.85 [0.65, 0.96]	1.00 [0.81, 1.00]
Adel 2014	24	0	2	24	0.92 [0.75, 0.99]	1.00 [0.86, 1.00]
El-Sherbiny 2015	49	1	3	67	0.94 [0.84, 0.99]	0.99 [0.92, 1.00]

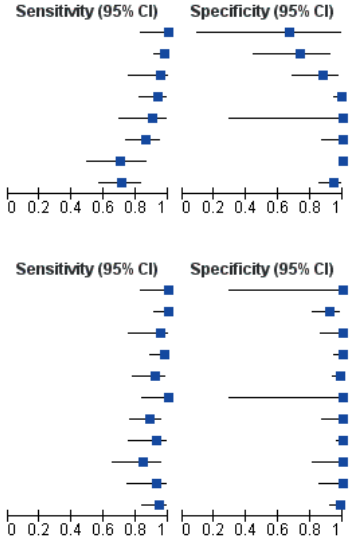


Figure 4. Forest plot of 2D SIS and 3D SIS; studies reporting abnormality or not.

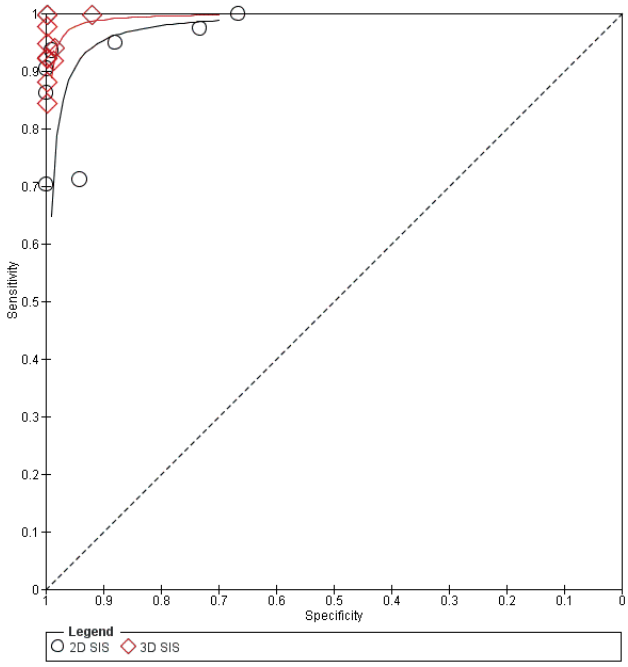


Figure 5. Summary ROC Plot of 2D SIS and 3D SIS.

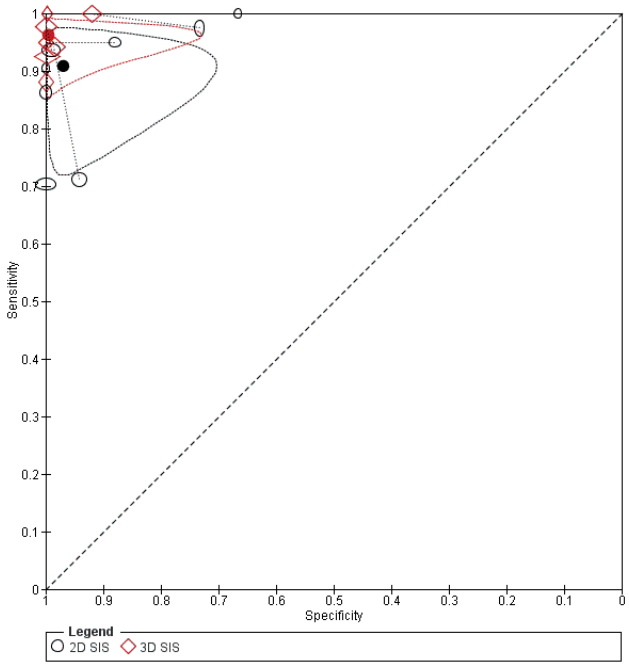


Figure 6. Summary ROC plot of 2D SIS and 3D SIS; sensitivity-specificity pairs from studies that studied both 2D SIS and 3D SIS are linked with a dashed line

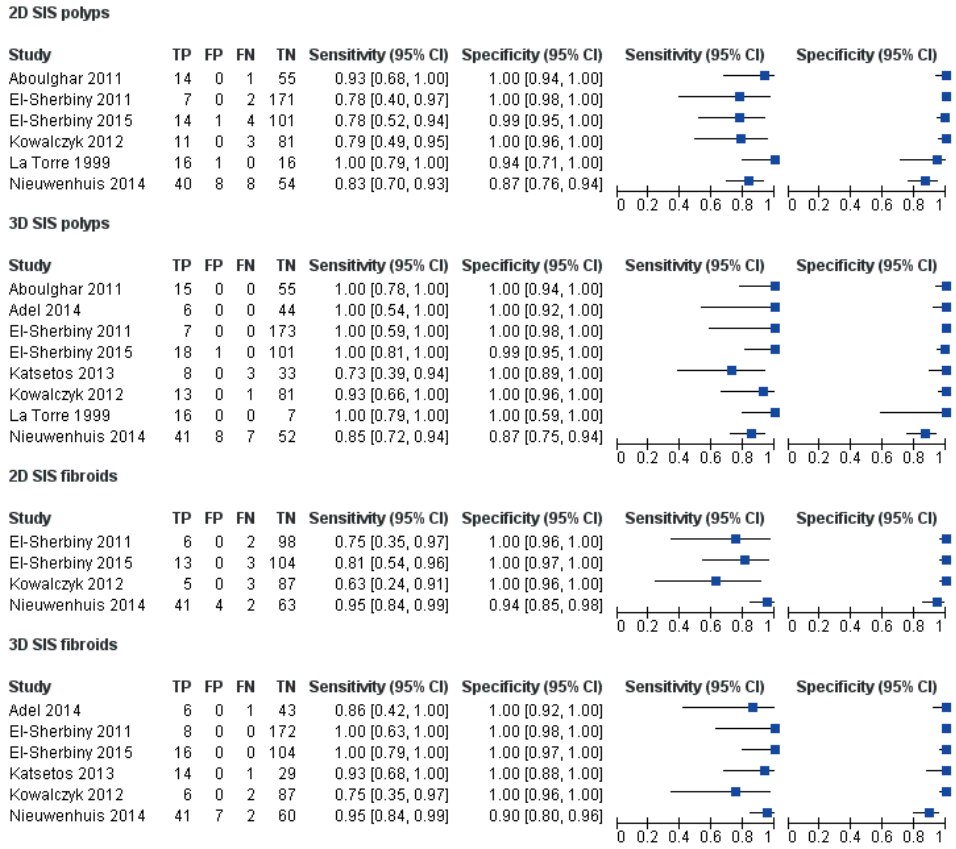


Figure 7. Forest plot of studies reporting type of abnormality (polyps and fibroids) for 2D SIS and 3D SIS.

Summary of findings table

Study question	Accuracy of 3-dimensional (3D) saline infusion sonography (SIS) compared with 2-dimensional (2D) SIS for the diagnosis of focal intracavitary abnormalities
Patient population	Premenopausal women with abnormal uterine bleeding or subfertility and postmenopausal women with abnormal uterine bleeding; 7 studies included patients with abnormal uterine bleeding, 3 included patients with subfertility and 3 included both types of patients
Prior testing	Eight of 13 studies reported a prior test. Prior tests reported were 2D ultrasonography and hysterosalpingography
Index tests	The review includes studies evaluating the diagnostic accuracy of 3D SIS (index test 1) and studies evaluating the diagnostic accuracy of 2D SIS+3D SIS (index test 2) in comparison with 2D SIS (comparator test)
Reference standard	Hysteroscopy was the reference standard
Target condition	Lesions focally growing inside the uterine cavity (anomalies of the uterine cavity were excluded)
Studies	The search included studies from inception until March 2016. Thirteen studies (1053 women) matched the inclusion criteria and were included for qualitative synthesis: 1 randomised controlled trial (RCT) and 12 prospective cohort studies. Eleven studies (846 women) reported accuracy in detecting presence/absence of an abnormality, and 8 studies reported presence/absence of a specific abnormality (uterine polyp or submucous fibroid). Study size ranged from 23 to 180 participants. Prevalence of the target condition ranged from 14% to 96%
Methodological quality concerns	The design of the included studies seems applicable. The main quality problem with the included studies was insufficient reporting of methods, resulting in unclear risk of bias for several of the quality domains assessed. Therefore, review authors considered the overall quality of the evidence as low
Main outcome	The summary estimate (11 studies reporting 3D SIS) for sensitivity was 94.5% (95% confidence interval (CI) 90.6% to 96.9%) and for specificity 99.4% (95% CI 96.2% to 99.9%) evaluated against hysteroscopy Meta-analysis of the 8 studies (N = 716) directly comparing 2D SIS vs 3D SIS showed no statistically significant difference (P values of 0.07 for sensitivity and 0.10 for specificity). Summary sensitivity of 3D SIS was approximately the same as in the complete set of 11 3D SIS studies: sensitivity 96.9% (95% CI 91.9% to 98.8%); specificity 99.5% (95% CI 96.1% to 100%). The summary sensitivity for 2D SIS was 90.9% (95% CI 81.2% to 95.8%) and for specificity 96.3% (95% CI 86.1% to 99.1%) To characterise the usefulness of the test in different prevalence scenarios, we calculated post-test probabilities (PPVs) for 3 different values of prevalence: 15%, 50% and 90%. PPV would be 96.0%, 99.3% and 99.9%, respectively. Sensitivity analyses showed nearly no influence on the summary estimates of sensitivity and specificity
Conclusion	Low-quality evidence showed 3D SIS to be very accurate in detecting intracavitary abnormalities. Meta-analysis showed no statistically significant differences between 2D SIS and 3D SIS. Summary sensitivity and specificity are higher for 3D SIS but margins of improvement are limited because 2D SIS is already very accurate. 3D SIS is an alternative to 2D SIS for which the technology and appropriate expertise are available. Both 2D SIS and 3D SIS should be considered alternatives to diagnostic hysteroscopy when intracavitary pathology is suspected in subfertile women and in those with abnormal uterine bleeding

Assessment of methodological quality; QUADAS-2 and additional questions

DOMAIN	PATIENT SELECTION	INDEX TESTS	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection Describe included participants (prior testing, presentation, setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted State the target condition	Describe any participants who did not receive the index test(s) and/or reference standard or who were excluded from the 2×2 table (refer to flow diagram) Describe the time interval and any interventions between index test(s) and reference standard
QUADAS-2 signalling questions (yes/no/ unclear)	Was a consecutive or random sample of participants enrolled? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of results of the reference standard? If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of results of the index test?	Was the interval between index test(s) and reference standard appropriate? Did all participants receive a reference standard? Did participants receive the same reference standard? Were all participants included in the analysis?
Additional signalling questions	How was participant recruitment arranged (based on presenting symptoms or results from a previous test)?	Was execution of the index test described sufficiently to permit replication of the test? Were criteria for different index test findings well defined? Were complications with the index test registered? Is the amount of experience/training of the persons executing and reading the index tests specified?	Was the target condition specified? Were complications with the reference standard registered? Is the amount of experience/ training of the persons executing and reading the reference test specified?	Was partial verification bias avoided? Were uninterpretable results reported? Were withdrawals explained?
Risk of bias (low/high/ unclear)	Could the selection of participants have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could participant flow have introduced bias?
Concerns regarding applicability (low/high/ unclear)	Are there concerns that included participants and setting do not match the review question?	Are there concerns that the index test, its conduct or its interpretation differs from the review question?	Is there concern that the target condition as defined by the reference standard does not match the review question?	

REFERENCES

Included studies

Aboulghar 2011. Aboulghar MM, Shoeir IK, Momtaz M, Mohammady ME, Ezzat H. A comparative study of 2-dimensional sonohysterography versus 3-dimensional sonohysterography in infertile patients with uterine cavity lesions and abnormalities. Middle East Fertility Society Journal 2011;16:67-71.

Adel 2014. Adel M, Kandil M, Abo-Elnasr M, Sanad Z, Farag H. Three-dimensional sonohysterography may replace hysteroscopy for women with perimenopausal bleeding. Climacteric 2014;17:55-9.

de Kroon 2004. de Kroon CD, Louwe LA, Trimbos JB, Jansen FW. The clinical value of 3-dimensional saline infusion sonography in addition to 2-dimensional saline infusion sonography in women with abnormal uterine bleeding: work in progress. Journal of Ultrasound in Medicine 2004;23:1433-40.

El-Sherbiny 2011. El-Sherbiny W, Nasr AS. Value of 3-dimensional sonohysterography in infertility work-up. Journal of Minimally Invasive Gynecology 2011;18:54-8.

El-Sherbiny 2015. El-Sherbiny W, El-Mazny A, Abou-Salem N, Mostafa WS. The diagnostic accuracy of two- vs three-dimensional sonohysterography for evaluation of the uterine cavity in the reproductive age. Journal of Minimally Invasive Gynecology 2015;22(1):127-31.

Katsetos 2013. Katsetos C, Radhakrishnan S, Koumousidis A, Kontoyannis M, Sanoulis V, Spaliaras D, et al. Comparison of transvaginal 3D sonohysterography with outpatient hysteroscopy in the evaluation of abnormal uterine bleeding. Clinical & Experimental Obstetrics & Gynecology 2013;40:74-7.

Kowalczyk 2012. Kowalczyk D, Guzikowski W, Wiecek J, Sioma-Markowska U. Clinical value of real time 3D sonohysterography and 2D sonohysterography in comparison to hysteroscopy with subsequent histopathological examination in perimenopausal women with abnormal uterine bleeding. Neuroendocrinology Letters 2012;33:212-6.

Kupesic 2007. Kupesic S, Plavsic BM. 2D and 3D hysterosalpingo-contrast-sonography in the assessment of uterine cavity and tubal patency. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2007;133:64-9.

La Torre 1999. La Torre R, De Felice C, De Angelis C, Coacci F, Mastrone M, Cosmi EV. Transvaginal sonographic evaluation of endometrial polyps: a comparison with two dimensional and three dimensional contrast sonography. Clinical & Experimental Obstetrics & Gynecology 1999;26:171-3.

Makris 2007. Makris N, Kalmantis K, Skartados N, Papadimitriou A, Mantzaris G, Antsaklis A. Three-dimensional hysterosonography versus hysteroscopy for the detection of intracavitary uterine abnormalities. International Journal of Gynaecology & Obstetrics 2007;97:6-9.

Nieuwenhuis 2014. Nieuwenhuis LL, de Vaate MA, Hehenkamp WJ, Heymans MW, van Baal MW, Brolmann HA, et al. Diagnostic and clinical value of 3D gel installation sonohysterography in addition to 2D gel installation sonohysterography in the assessment of intrauterine abnormalities. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2014;175:67-74.

Sconfienza 2010. Sconfienza LM, Lacelli F, Caldiera V, Perrone N, Piscopo F, Gandolfo N, et al. Three-dimensional sonohysterography for examination of the uterine cavity in women with abnormal uterine bleeding: preliminary findings. Journal of Ultrasound 2010;13:16-21.

Sylvestre 2003. Sylvestre C, Child TJ, Tulandi T, Tan SL. A prospective study to evaluate the efficacy of two- and three-dimensional sonohysterography in women with intrauterine lesions. Fertility & Sterility 2003;79:1222-5.

Excluded studies

Abou-Salem 2010. Abou-Salem N, Elmazny A, El-Sherbiny W. Value of 3-dimensional sonohysterography for detection of intrauterine lesions in women with abnormal uterine bleeding. Journal of Minimally Invasive Gynecology 2010;17:200-4.

Ahmad 2014. Ahmad RA, Sadek SM, Ragheb AS. Evaluation of the uterine cavity by magnetic resonance imaging, three dimensional hysterosonography and diagnostic hysteroscopy in women with pre- and post-menopausal bleeding. Middle East Fertility Society Journal 2015;20:70-8.

Ahmadi 2013. Ahmadi F, Rashidy Z, Haghighi H, Akhoond M, Niknejadi M, Hemat M, et al. Uterine cavity assessment in infertile women: sensitivity and specificity of three-dimensional hysterosonography versus hysteroscopy. Iranian Journal of Reproductive Medicine 2013;11:977-82.

Ayida 1996. Ayida G, Kennedy S, Barlow D, Chamberlain P. Contrast sonography for uterine cavity assessment: a comparison of conventional two-dimensional with three-dimensional transvaginal ultrasound; a pilot study. Fertility & Sterility 1996;66:848-50.

Ayoubi 2002. Ayoubi JM, Fanchin R, Ferretti G, Pons JC, Bricault I. Three-dimensional ultrasonographic reconstruction of the uterine cavity: toward virtual hysteroscopy? European Radiology 2002;12:2030-3.

Jurisic 2013. Jurisic A, Jurisic Z, Garalejic E, Arsic B, Jankovic-Raznatovic S, Arsic V. 3D multislice saline infusion sonography in preoperative evaluation of endometrial cavity. Giornale Italiano di Ostetricia e Ginecologia 2013;35:232-7.

Khan 2011. Khan F, Jamaat S, Al-Jaroudi D. Saline infusion sonohysterography versus hysteroscopy for uterine cavity evaluation. Annals of Saudi Medicine 2011;31:387-92.

Lagana 2014. Laganà AS, Ciancimino L, Mancuso A, Chiofalo B, Rizzo P, Triolo O. 3D sonohysterography vs hysteroscopy: a cross-sectional study for the evaluation of endouterine diseases. Archives of Gynecology and Obstetrics 2014;290(6):1173-8.

Makris 2005. Makris N, Kalmantis K, Skartados N, Xatzipappas J, Antsaklis A. Three-dimensional hysterosonography for the study of the endometrial cavity in infertile women: comparison with diagnostic hysteroscopy. Gynecological Surgery 2005;2:S42.

Makris 2007a. Makris N, Skartados N, Kalmantis K, Mantzaris G, Papadimitriou A, Antsaklis A. Evaluation of abnormal uterine bleeding by transvaginal 3-D hysterosonography and diagnostic hysteroscopy. European Journal of Gynaecological Oncology 2007;28:39-42.

Mora-Guanche 2009. Mora-Guanche P, Sparacino L, Garcia-Guzman R, Bennett RA, Hernandez J, Palumbo A. Three-dimensional sonohysterography (SHG) has improved diagnostic accuracy for intrauterine pathology compared to two-dimensional SHG: a prospective pilot study in infertility patients. Fertility & Sterility 2009;1:S119.

Mora-Guanche 2010. Mora-Guanche P, Garcia-Guzman R, Bennett R, Iaconianni L, Hernandez J, Palumbo A. Diagnostic accuracy of three dimensional sonohysterography (SHG) for intrauterine abnormalities in infertility compared to two dimensional SHG. Human Reproduction 2010;25:i332.

Additional references

Abou Salem 2010. Abou-Salem N, Elmazny A, El-Sherbiny W. Value of 3-dimensional sonohysterography for detection of intrauterine lesions in women with abnormal uterine bleeding. Journal of Minimally Invasive Gynecology 2010;17(2):200-4.

Beemsterboer 2008. Beemsterboer SN, Thurkow AL, Verstraeten R, Brolmann HA. Reproducibility of saline contrast sonohysterography for the detection of intracavitary abnormalities in women with abnormal uterine bleeding. Ultrasound in Obstetrics & Gynecology 2008;31(4):445-9. [PubMed: 18383471]

Betjes 2009. Betjes HE, Hanstede MM, Emanuel MH, Stewart EA. Hysteroscopic myomectomy and case volume hysteroscopic myomectomy performed by high- and low-volume surgeons. The Journal of Reproductive Medicine 2009;54(7):425-8. [PubMed: 19691258]

Bij de Vaate 2010. Bij de Vaate AJ, Brolmann HA, van der Slikke JW, Emanuel MH, Huirne JA. Gel instillation sonohysterography (GIS) and saline contrast sonohysterography (SCSH): comparison of two diagnostic techniques. Ultrasound in Obstetrics & Gynecology 2010;35(4):486-9. [PubMed: 20178106]

Bosteels 2015. Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD009461. DOI: 10.1002/14651858.CD009461.pub3.

Cohen 2015. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 2016;6(11).

de Kroon 2003. de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG 2003;110(10):938-47. [PubMed: 14550365]

Dijkhuizen 2003. Dijkhuizen FP, Mol BW, Bongers MY, Brolmann HA, Heintz AP. Cost-effectiveness of transvaginal sonography and saline infused sonography in the evaluation of menorrhagia. International Journal of Gynaecology and Obstetrics 2003;83(1):45-52. [PubMed: 14511871]

Dongen 2011. van Dongen H, Timmermans A, Jacobi CE, Elskamp T, de Kroon CD, Jansen FW. Diagnostic hysteroscopy and saline infusion sonography in the diagnosis of intrauterine abnormalities: an assessment of patient preference. Gynecological Surgery 2011;8(1):65-70.

Emanuel 1995. Emanuel MH, Verdel MJ, Wamsteker K, Lammes FB. A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding: clinical implications. American Journal of Obstetrics and Gynecology 1995;172(2 Pt 1):547-52. [Other:]

Fatemi HM 2010. Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P, et al. Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. Human Reproduction 2010;25(8):1959-65. [PubMed: PUBMED 20570971]

Gath 1987. Gath D, Osborn M, Bungay G, Iles S, Day A, Bond A. Psychiatric disorder and gynaecological symptoms in middle aged women: a community survey. British Medical Journal (Clin Res Ed) 1987 Jan 24;294(6566):213-8. [PubMed: PMID: 3101815]

Golan 2001. Golan A, Sagiv R, Berar M, Ginath S, Glezerman M. Bipolar electrical energy in physiologic solution - a revolution in operative hysteroscopy. Journal of the American Association of Gynecologic Laparoscopists 2001;8(2):252-8.

Guideline ACOG. ACOG technology assessment no. 8: Sonohysterography. Obstetrics and Gynecology 2012;119(6):1325. [DOI: 10.1097/AOG.0b013e31825af435.]

Guideline NVOG. Dr. W.J.K. Hehenkamp, gynaecoloog, NVOG (voorzitter). Heavy menstrual bleeding [Hevig menstrueel bloedverlies]. Guideline NVOG 2013;1-196. [Other: http://nvog-documenten.nl/uploaded/docs/Richtlijn%20Hevig%20Menstrueel%20Bloedverlies%20ws%202013.pdf]

Guideline RCOG. National Institute for Health and Care Excellence (NICE). Heavy menstrual bleeding: assessment and management. NICE clinical guideline 44 2007, last updated: August 2016. [Other: https://www.nice.org.uk/guidance/cg44/resources/heavy-menstrual-bleeding-assessment-and-management-975447024325]

Guideline SOGC. Singh S Best C Dunn S, Leyland N, Wolfman WL; Clinical Practice – Gynaecology Committee, Leyland N, Wolfman W, Allaire C, Awadalla A, Best C, Dunn S, Heywood M, Lemyre M, Marcoux V, Menard C, Potestio F, Rittenberg D, Singh S; Society of Obstetricians and Gynaecologists of Canada.. Abnormal uterine bleeding in pre-menopausal women.

SOGC CLINICAL PRACTICE GUIDELINES May 2013 (Replaces Aug 2001);No. 292 (Replaces No. 106, Aug 2001):1-32. [Other: https://sogc.org/wp-content/uploads/2013/01/106E-CPG-August2001.pdf]

Guyatt. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

Klatsky 2008. Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. American Journal of Obstetrics and Gynecology 2008;198(4):357.

Kroon 2006. Kroon CD, Jansen FW. Saline infusion sonography in women with abnormal uterine bleeding: an update of recent findings. Current Opinion in Obstetrics and Gynecology 2006;18(6):653-7.

Lee 2006. Lee C, Salim R, Ofili-Yebovi D, Yazbek J, Davies A, Jurkovic D. Reproducibility of the measurement of submucous fibroid protrusion into the uterine cavity using three-dimensional saline contrast sonohysterography. Ultrasound in Obstetrics & Gynecology 2006;28(6):837-41. [PubMed: 17019741]

Leeflang 2008. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. Annals of Internal Medicine 2008;149(12):889-97. [PubMed: 19075208]

Lethaby 2002. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. BJOG. 2002;109(10):108-9.

Liu 2007. Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. Value Health 2007;10(3):183-9.

Mavrelos 2011. Mavrelos D, Naftalin J, Hoo W, Ben-Nagi J, Holland T, Jurkovic D. Preoperative assessment of submucous fibroids by three-dimensional saline contrast sonohysterography. Ultrasound in Obstetrics & Gynecology 2011;38(3):350-4. [PubMed: 21584888]

Metello 2008. Metello J, Relva A, Milheras E, Colaco J, Retto H. Hysteroscopic diagnostic accuracy in post-menopausal bleeding. Acta Medica Portuguesa 2008;21(5):483-8.

Munro 2011. Munro MG, Critchley HO, Fraser IS; FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility 2011;95(7):2204-8.

Parsons 1993. Parsons AK, Lense JJ. Sonohysterography for endometrial abnormalities: preliminary results. Journal of Clinical Ultrasound 1993;21(2):87-95.

Patterson 1994. Patterson-Keels LM, Selvaggi SM, Haefner HK, Randolph JF Jr. Morphologic assessment of endometrium overlying submucosal leiomyomas. Journal of Reproductive Medicine 1994;39(8):579..

Pritts 2009. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertility & Sterility 2009;91(4):1215..

Reitsma 2005. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of Clinical Epidemiology 2005;58(10):982-90. [PubMed: 16168343]

Salim 2005. Salim R, Lee C, Davies A, Jolaoso B, Ofuasia E, Jurkovic D. A comparative study of three-dimensional saline infusion sonohysterography and diagnostic hysteroscopy for the classification of submucous fibroids. Human Reproduction 2005;20(1):253-7.

Sancho 2016. Sancho JM, Delgado VS, Valero MJ, Soteras MG, Amate VP, Carrascosa AA. Hysteroscopic myomectomy outcomes after 3-month treatment with either Ulipristal Acetate or GnRH analogues: a retrospective comparative study. European Journal of Obstetric and Gynecologic Reproductive Biology 2016;198:127-30.

Santer 2005. Santer M, Warner P, Wyke S. A Scottish postal survey suggested that the prevailing clinical preoccupation with heavy periods does not reflect the epidemiology of reported symptoms and problems. Journal of Clinical Epidemiology 2005;58(11):1206-10.

Stewart 1996. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Human Reproduction Update 1996;2(4):295.

Takwoingi 2015. Takwoingi Y, Guo B, Riley RD, Deeks JJ. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. Statistical Methods in Medical Research 2015 Jun 26. [PubMed: pii: 0962280215592269]

Tarneja 2002. Tarneja P, Dugal BS. Hysteroscopy: past, present and future. Medical Journal of Armed Forces India 2002;58(4):293-4.

Terry 2009. Terry S, Banks E, Harris K, Duvivier R, Dar P. Comparison of 3-dimensional with 2-dimensional saline infusion sonohysterograms for the evaluation of intrauterine abnormalities. Journal of Clinical Ultrasound 2009;37(5):258-62. [PubMed: 19208422]

Tur-Kaspa 2006. Tur-Kaspa I, Gal M, Hartman M, Hartman J, Hartman A. A prospective evaluation of uterine abnormalities by saline infusion sonohysterography in 1,009 women with infertility or abnormal uterine bleeding. Fertility & Sterility 2006;86(6):1731-5. [PubMed: 17007850]

van den Bosch 2008. Van den Bosch T, Verguts J, Daemen A, Gevaert O, Domali E, Claerhout F. Pain experienced during transvaginal ultrasound, saline contrast sonohysterography, hysteroscopy and office sampling: comparative study. Ultrasound in Obstetrics & Gynecology 2008;31:346-51.

van den Bosch 2015. Van den Bosch T, Ameye L, Van Schoubroeck D, Bourne T, Timmerman D. Intra-cavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. Facts, Views & Visions in Obgyn 2015;7(1):17–24.

van den Bosch 2015a. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound in Obstetrics & Gynecology 2015;46(3):284-98.

van Dongen 2007. van Dongen H, de Kroon CD, Jacobi CE, Trimbos JB, Jansen FW. Diagnostic hysteroscopy in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG 2007;114(6):664-75.

van Hanegem 2011. van Hanegem N, Breijer MC, Khan KS, Clark TJ, Burger MP, Mol BW, et al. Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. Maturitas 2011;68(2):155-64.

van Hanegem 2016. van Hanegem N, Breijer MC, Slockers SA, Zafarmand MH, Geomini P, Catshoek R, et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. BJOG 2017;124(2):231-40.

Wamsteker 1993. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstetrics and Gynecology 1993;82(5):736-40. [PubMed: 8414318]

Werbrouck 2011. Werbrouck E, Veldman J, Luts J, Van Huffel S, Van Schoubroeck D, Timmerman D, et al. Detection of endometrial pathology using saline infusion sonography versus gel instillation sonography: a prospective cohort study. Fertility & Sterility 2011;95(1):285-8.

Whiting 2011. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine 2011;155(8):529-36.

Widrich 1996. Widrich T, Bradley LD, Mitchinson AR, Collins RL. Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium. American Journal of Obstetrics and Gynecology 1996;174(4):1327-34.

DATA AND ANALYSES

Data tables by test

TEST	STUDIES	PARTICIPANTS
1 2D SIS	8	716
2 3D SIS	11	846
3 2D SIS polyps	6	608
4 3D SIS polyps	8	690
5 2D SIS fibroids	4	431
6 3D SIS fibroids	6	599
7 2D+3D SIS polyps	1	123
8 2D+3D SIS fibroids	1	117

Sources of support

Internal sources

- VU University Medical Center, Netherlands

APPENDICES

1 CENTRAL CRSO search strategy

Searched 01 March 2016

WEB platform

#1 MESH DESCRIPTOR Imaging, Three-Dimensional EXPLODE ALL TREES (928)
#2 ((Three-Dimensional and imag*)):TI,AB,KY (1511)
#3 ((3D and imag*)):TI,AB,KY (843)
#4 ((3 D and imag*)):TI,AB,KY (159)
#5 ((Three-Dimensional and sonogra*)):TI,AB,KY (30)
#6 ((3D and sonogra*)):TI,AB,KY (22)
#7 ((3 D and sonogra*)):TI,AB,KY (3)
#8 ((Three-Dimensional and sonohysterogra*)):TI,AB,KY (6)
#9 ((3D and sonohysterogra*)):TI,AB,KY (7)
#10 ((Three-Dimensional and SIS)):TI,AB,KY (2)
#11 ((3D and SIS)):TI,AB,KY (2)
#12 3dus:TI,AB,KY (8)
#13 (3 dus):TI,AB,KY (1)
#14 ((Three-Dimensional and ultraso*)):TI,AB,KY (312)
#15 ((3D and ultraso*)):TI,AB,KY (189)
#16 ((3 D and ultraso*)):TI,AB,KY (46)
#17 (3D US):TI,AB,KY (16)
#18 ((Three-Dimensional and hystero*)):TI,AB,KY (13)
#19 ((3D and hystero*)):TI,AB,KY (10)
#20 ((3 D and hystero*)):TI,AB,KY (2)
#21 (three dimension):TI,AB,KY (14)
#22 (3 dimension):TI,AB,KY (4)
#23 ((3d and multiplanar)):TI,AB,KY (14)
#24 ((3 dimension* and multiplanar)):TI,AB,KY (3)
#25 ((three dimension* and multiplanar)):TI,AB,KY (23)
#26 ((three dimensional or 3d or 3 d)):TI,AB,KY (4347)
#27 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 (4368)
#28 MESH DESCRIPTOR Ultrasonography EXPLODE ALL TREES (7718)
#29 MESH DESCRIPTOR Endosonography EXPLODE ALL TREES (271)
#30 #28 OR #29 (7718)
#31 1990 TO 2016:YR (777345)
#32 #30 AND #31 (7262)
#33 #27 OR #32 (11430)
#34 ((uter* adj2 abnormal*)):TI,AB,KY (89)
#35 ((abnormal vagina* bleeding)):TI,AB,KY (15)
#36 ((intrauter* adj2 patholog*)):TI,AB,KY (13)
#37 (intrauter* adj2 abnormal*):TI,AB,KY (16)
#38 (endometri* adj2 abnormal*):TI,AB,KY (47)
#39 (uter* adj2 anomal*):TI,AB,KY (22)
#40 (endometri* adj2 anomal*):TI,AB,KY (1)
#41 (intrauterine adj2 anomal*):TI,AB,KY (1)
#42 (dysfunctional uter* bleeding):TI,AB,KY (121)
#43 DUB:TI,AB,KY (28)
#44 (heavy menstrual bleed*):TI,AB,KY (101)
#45 (postmenopaus* adj2 bleed*):TI,AB,KY (42)
#46 (perimenopaus* adj2 bleed*):TI,AB,KY (2)
#47 MESH DESCRIPTOR Menorrhagia EXPLODE ALL TREES (261)
#48 MESH DESCRIPTOR Metrorrhagia EXPLODE ALL TREES (77)
#49 (uter* adj2 h?emorrhag*):TI,AB,KY (558)
#50 menorrhagi*:TI,AB,KY (531)
#51 metrorrhagi*:TI,AB,KY (201)
#52 (endometri* adj2 lesion*):TI,AB,KY (56)
#53 (endometri* adj2 adhesion*):TI,AB,KY (19)

#54 (uter* adj2 lesion*):TI,AB,KY (10)
#55 (uter* adj2 adhesion*):TI,AB,KY (15)
#56 (intrauter* adj2 adhesion*):TI,AB,KY (27)
#57 (ovar* adj2 adhesion*):TI,AB,KY (12)
#58 (intrauter* adj2 lesion*):TI,AB,KY (15)
#59 polyp*:TI,AB,KY (5147)
#60 endometrio*:TI,AB,KY (1214)
#61(adnexal mass*):TI,AB,KY (36)
#62 MESH DESCRIPTOR Adenomyosis EXPLODE ALL TREES (5)
#63 adenomyosis:TI,AB,KY (65)
#64 MESH DESCRIPTOR Leiomyoma EXPLODE ALL TREES (409)
#65 myoma*:TI,AB,KY (443)
#66 infertil*:TI,AB,KY (3628)
#67 subfertil*:TI,AB,KY (492)
#68 leiomyoma*:TI,AB,KY (511)
#69 fibroid*:TI,AB,KY (350)
#70 (arcuate uter*):TI,AB,KY (2)
#71 (endometri* adj2 thick*):TI,AB,KY (716)
#72 (uter* adj2 malformation*):TI,AB,KY (25)
#73 (bicornuate adj2 uterus):TI,AB,KY (2)
#74 (intracavity abnormal*):TI,AB,KY (1)
#75 (uter* adj2 contour):TI,AB,KY (0)
#76 (uter* adj3 sept*):TI,AB,KY (29)
#77 (endometri* adj2 atroph*):TI,AB,KY (54)
#78 (endometri* adj2 tumo?r*):TI,AB,KY (64)
#79 (uter* adj2 malignan*):TI,AB,KY (14)
#80 (uter* adj2 cancer*):TI,AB,KY (548)
#81 (endometri* adj2 malignan*):TI,AB,KY (15)
#82 (endometri* adj2 cancer*):TI,AB,KY (595)
#83 (ovar* adj2 malignan*):TI,AB,KY (35)
#84 (ovar* adj2 cancer*):TI,AB,KY (2465)
#85 (uter* adj2 disorder*):TI,AB,KY (6)
#86 (uter* adj2 disease*):TI,AB,KY (423)
#87 (endometri* adj2 neoplasm*):TI,AB,KY (317)
#88 (uter* adj2 neoplasm*):TI,AB,KY (1945)
#89 (uter* adj2 patholog*):TI,AB,KY (509)
#90 (endometr* adj2 patholog*):TI,AB,KY (518)
#91 MESH DESCRIPTOR Adenomyoma EXPLODE ALL TREES (3)
#92 Adenomyoma*:TI,AB,KY (8)
#93 fibroma*:TI,AB,KY (37)
#94 fibromyoma*:TI,AB,KY (11)
#95 MESH DESCRIPTOR Infertility, Female EXPLODE ALL TREES (1025)
#96 MESH DESCRIPTOR Endometriosis EXPLODE ALL TREES (505)
#97 MESH DESCRIPTOR Uterine Diseases EXPLODE ALL TREES (3708)
#98 MESH DESCRIPTOR Polyps EXPLODE ALL TREES (642)
#99 MESH DESCRIPTOR Endometrial Hyperplasia EXPLODE ALL TREES (106)
#100 (Endometri* adj3 Hyperplas*):TI,AB,KY (333)
#101 MESH DESCRIPTOR Ovarian Diseases EXPLODE ALL TREES (2425)
#102 (Ovar* adj2 Disease*):TI,AB,KY (639)
#103 (ovar* adj2 mass*):TI,AB,KY (20)
#104 (ovar* adj2 cyst*):TI,AB,KY (285)
#105 (ovar* adj2 tumo?r*):TI,AB,KY (139)
#106 MESH DESCRIPTOR Gynecology EXPLODE ALL TREES (105)
#107 Gyn?ecology:TI,AB,KY (1901)
#108 (uter* cavit*):TI,AB,KY (234)
#109 (endometrial cavity):TI,AB,KY (44)
#110 (intracav* lesion*):TI,AB,KY (2)
#111 (intracav* abnormal*):TI,AB,KY (4)
#112 (uter* adj2 volume*):TI,AB,KY (162)
#113 (ovar* adj2 volume*):TI,AB,KY (98)
#114 #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97

OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 (20885)
#115 #33 AND #114 (326)

2 Clinicaltrials.gov search strategy

Searched 01 March 2016
Intracavitary abnormality or sonohysterography
1 hit

3 ICTRP search strategy

Searched 01 March 2016
Intracavitary abnormality or sonohysterography
19 hits

4 PubMed search strategy

Searched 01 March 2016

((("ultrasonography" [Subheading] OR "Ultrasonography"[Mesh] OR "Hysterosalpingography"[Mesh] OR ((ultrasonograph*[tiab] OR ultrasound[tiab] OR sonograph*[tiab] OR sonohysterograph*[tiab] OR hysterosonograph*[tiab]) AND (transvagina*[tiab] OR saline[tiab] OR gel[tiab] OR infusion[tiab] OR instillation[tiab] OR contrast[tiab] OR enhanced[tiab])) OR sonohysterosalpingograph*[tiab] OR hysterosonosalpingograph*[tiab] OR hysterosalpingosonograph*[tiab] OR gis[tiab] OR sis[tiab] OR shsg[tiab] OR hssg[tiab] OR shg[tiab] OR HyCoSy[tiab] OR tvs[tiab])) AND ("Imaging, Three-Dimensional"[Mesh:NoExp] OR threedimension*[tiab] OR "3 d"[tiab] OR 3d[tiab] OR 3dus[tiab] OR "3 dus"[tiab] OR 3dimension*[tiab] OR ((three[tiab] OR 3[tiab]) AND dimension*[tiab]))) AND (menorrhagi*[tiab] OR metrorrhagi*[tiab] OR infertil*[tiab] OR polyp[tiab] OR polyps[tiab] OR ((bleeding*[tiab] OR hemorrhag*[tiab]) AND (vagina*[tiab] OR uterus[tiab] OR uterine[tiab] OR disorder*[tiab] OR postmenopausal[tiab] OR premenopausal[tiab])) OR ((abnormalit*[tiab] OR lesion*[tiab] OR disease[tiab] OR diseases[tiab] OR diseased[tiab] OR patholog*[tiab] OR disorder*[tiab]) AND (uterine[tiab] OR uterus[tiab] OR cavum[tiab] OR cavity[tiab] OR intracavit*[tiab] OR intrauterine[tiab] OR endometri*[tiab])) OR myoma*[tiab] OR leiomyoma*[tiab] OR adenomyoma*[tiab] OR (fibroid*[tiab] AND (uterus[tiab] OR uterine[tiab])) OR fibroma*[tiab] OR fibromyoma*[tiab] OR "Leiomyoma"[Mesh] OR "Myoma"[Mesh:NoExp] OR "Uterine Hemorrhage"[Mesh] OR "Infertility, Female"[Mesh] OR "Polyps"[Mesh:NoExp])

756 hits

5 MEDLINE search strategy

From inception until 01 March 2016
OVID platform

1 (uter$ adj2 abnormal$).tw. (2567)
2 abnormal vagina$ bleeding.tw. (478)
3 (intrauter$ adj2 abnormal$).tw. (291)
4 (endometri$ adj2 abnormal$).tw. (629)
5 (uterine adj2 anomal$).tw. (565)
6 (endometri$ adj2 anomal$).tw. (34)
7 (intrauterine adj2 anomal$).tw. (88)
8 (uterine adj2 anomal$).tw. (565)
9 abnormal uter$ bleeding.tw. (1505)
10 dysfunctional uter$ bleeding.tw. (800)
11 DUB.tw. (675)
12 heavy menstrual bleeding.tw. (482)

13 (postmenopaus$ adj2 bleed$).tw. (1022)
14 (perimenopaus$ adj2 bleed$).tw. (58)
15 exp uterine hemorrhage/ (18508)
16 uter$ haemorrhag$.tw. (136)
17 uter$ hemorrhag$.tw. (565)
18 menorrhagi$.tw. (2838)
19 metrorrhagi$.tw. (1007)
20 (endometri$ adj2 lesion$).tw. (2070)
21 (endometri$ adj2 adhesion$).tw. (320)
22 (uter$ adj2 lesion$).tw. (560)
23 (uter$ adj2 adhesion$).tw. (229)
24 (ovar$ adj2 adhesion$).tw. (177)
25 (intrauter$ adj2 adhesion$).tw. (348)
26 (intrauter$ adj2 lesion$).tw. (122)
27 polyp$.tw. (228328)
28 endometrio$.tw. (22928)
29 adnexal mass$.tw. (1959)
30 adenomyosis.tw. (1935)
31 exp leiomyoma/ or exp myoma/ (20495)
32 infertil$.tw. (46817)
33 subfertil$.tw. (3932)
34 myoma$.tw. (4946)
35 leiomyoma$.tw. (11503)
36 fibroid$.tw. (4746)
37 (septate adj2 uterus).tw. (357)
38 arcuate uter$.tw. (64)
39 (endometri$ adj2 thick$).tw. (2307)
40 (uter$ adj2 malformation$).tw. (636)
41 (bicornuate adj2 uterus).tw. (419)
42 intracavity abnormal$.tw. (2)
43 (uter$ adj2 contour).tw. (27)
44 (uter$ adj3 sept$).tw. (780)
45 endometri$ atroph$.tw. (208)
46 (endometri$ adj2 tumor$).tw. (1626)
47 (endometri$ adj2 tumour$).tw. (223)
48 ((uter$ adj2 malignan$) or (uter$ adj2 cancer$)).tw. (6004)
49 ((endometri$ adj2 malignan$) or (endometri$ adj2 cancer$)).tw. (13969)
50 ((ovar$ adj2 malignan$) or (ovar$ adj2 cancer$)).tw. (43226)
51 (uterus adj2 disorder$).tw. (4)
52 (uterine adj2 disorder$).tw. (167)
53 (uterus adj2 disease$).tw. (49)
54 (uterine adj2 disease$).tw. (594)
55 (endometri$ adj2 neoplasm$).tw. (254)
56 (uterine adj2 neoplasm$).tw. (377)
57 (uterus adj2 neoplasm$).tw. (16)
58 (uterine adj2 patholog$).tw. (590)
59 (uterus adj2 patholog$).tw. (62)
60 (endometri$ adj2 patholog$).tw. (1045)
61 Adenomyoma/ (422)
62 Adenomyo$.tw. (2933)
63 fibroma.tw. (6129)
64 fibromyoma$.tw. (700)
65 Infertility, Female/ (25115)
66 exp endometriosis/ or exp uterine diseases/ (163912)
67 Polyps/ (9807)
68 Endometrial Hyperplasia/ (3143)
69 (Endometri$ adj3 Hyperplasia).tw. (3264)
70 exp Ovarian Diseases/ (96073)
71 (ovar$ adj2 mass$).tw. (1902)
72 (ovar$ adj2 tumo?r).tw. (6368)
73 (ovar$ adj2 cyst$).tw. (7209)
74 Gynecology/ (16898)
75 (gynecolog$ or gynaecolog$).tw. (75147)
76 uter$ cavit$.tw. (3334)

77 endometrial cavity.tw. (607)
78 intracav$ lesion$.tw. (49)
79 intracav$ abnormal$.tw. (27)
80 (uter$ adj2 volume).tw. (778)
81 (ovar$ adj2 volume$).tw. (961)
82 (intrauter$ adj2 patholog$).tw. (240)
83 or/1-82 (630584)
84 Imaging, Three-Dimensional/ (50364)
85 (Three-Dimensional and imag$).tw. (36577)
86 (3D and imag$).tw. (31111)
87 (3 D and imag$).tw. (6624)
88 (Three-Dimensional and sonogra$).tw. (1090)
89 (3D and sonogra$).tw. (821)
90 (3 D and sonogra$).tw. (134)
91 3dus.tw. (152)
92 3 dus.tw. (14)
93 (Three-Dimensional and ultraso$).tw. (5390)
94 (3D and ultraso$).tw. (4037)
95 (3 D and ultraso$).tw. (1410)
96 3D US.tw. (348)
97 three dimension.tw. (439)
98 3 dimension.tw. (118)
99 (3d and multiplanar).tw. (843)
100 (3 dimension$ and multiplanar).tw. (183)
101 (three dimension$ and multiplanar).tw. (1112)
102 (three dimensional or 3d or 3 d).ti,ab,hw. and us.fs. (9851)
103 or/84-102 (95836)
104 Ultrasonography/ (64239)
105 limit 104 to yr="1990 -Current" (24736)
106 103 or 105 (119036)
107 (3D and hystero$).tw. (103)
108 (3 D and hystero$).tw. (18)
109 (Three-Dimensional and sonohysterogra$).tw. (33)
110 (3D and sonohysterogra$).tw. (26)
111 (3 D and sonohysterogra$).tw. (2)
112 (Three-Dimensional and SIS).tw. (59)
113 (3D and SIS).tw. (38)
114 (3 D and SIS).tw. (9)
115 (Three-Dimensional and hystero$).tw. (119)
116 (3d and hycosy).tw. (8)
117 (3 d and hycosy).tw. (2)
118 (three dimension$ and hycosy).tw. (11)
119 or/107-118 (252)
120 83 and 106 (3693)
121 119 or 120 (3797)
122 exp animals/ not humans.sh. (4191570)
123 121 not 122 (3658)

6 Embase search strategy

From inception until 01 March 2016

OVID platform

1 (uter$ adj2 abnormal$).tw. (3744)
2 (intrauter$ adj2 abnormal$).tw. (425)
3 (endometri$ adj2 abnormal$).tw. (856)
4 (uterine adj2 anomalies).tw. (713)
5 (endometri$ adj2 anomal$).tw. (47)
6 (intrauterine adj2 anomal$).tw. (130)
7 (uterine adj2 anomal$).tw. (935)
8 abnormal uter$ bleeding.tw. (2303)
9 dysfunctional uter$ bleeding.tw. (1024)

10 abnormal vagina$ bleeding.tw. (605)
11 DUB.tw. (903)
12 heavy menstrual bleeding.tw. (802)
13 intrauterine patholog$.tw. (321)
14 adnexal mass$.tw. (2850)
15 (uter$ adj2 malformation$).tw. (897)
16 exp uterus bleeding/ or uterine body disease/ (8339)
17 exp menorrhagia/ or "menorrhagia and metrorrhagia"/ (7890)
18 uter$ haemorrhag$.tw. (100)
19 uter$ hemorrhag$.tw. (535)
20 menorrhagi$.tw. (4288)
21 metrorrhagi$.tw. (1103)
22 (endometri$ adj2 lesion$).tw. (3052)
23 (endometri$ adj2 adhesion$).tw. (486)
24 (uter$ adj2 lesion$).tw. (723)
25 (uter$ adj2 adhesion$).tw. (322)
26 (intrauter$ adj2 lesion$).tw. (180)
27 (intrauter$ adj2 adhesion$).tw. (522)
28 polyp$.tw. (254616)
29 arcuate uter$.tw. (142)
30 endometrio$.tw. (32437)
31 endometrial cavity.tw. (896)
32 (endometri$ adj2 chang$).tw. (1164)
33 exp leiomyoma/ (15057)
34 exp uterus myoma/ or exp myoma/ (13856)
35 infertil$.tw. (62858)
36 subfertil$.tw. (5079)
37 myoma$.tw. (6767)
38 fibroid$.tw. (7555)
39 leiomyoma$.tw. (14056)
40 (septate adj2 uterus).tw. (561)
41 (bicornuate adj2 uterus).tw. (576)
42 intracavity abnormal$.tw. (2)
43 (uter$ adj2 contour).tw. (49)
44 (uter$ adj3 sept$).tw. (1227)
45 endometri$ atroph$.tw. (260)
46 (endometri$ adj2 tumor$).tw. (2126)
47 (endometri$ adj2 tumour$).tw. (316)
48 ((uter$ adj2 malignan$) or (uter$ adj2 cancer$)).tw. (7271)
49 ((endometri$ adj2 malignan$) or (endometri$ adj2 cancer$)).tw. (19880)
50 ((ovar$ adj2 malignan$) or (ovar$ adj2 cancer$)).tw. (58966)
51 (uterus adj2 disorder$).tw. (10)
52 (uterine adj2 disorder$).tw. (232)
53 (uterus adj2 disease$).tw. (78)
54 (uterine adj2 disease$).tw. (771)
55 (endometri$ adj2 neoplasm$).tw. (291)
56 (uterine adj2 neoplasm$).tw. (415)
57 (uterus adj2 neoplasm$).tw. (19)
58 (uterine adj2 patholog$).tw. (930)
59 (uterus adj2 patholog$).tw. (94)
60 (endometri$ adj2 patholog$).tw. (1561)
61 (endometri$ adj2 thick$).tw. (3739)
62 exp adenomyoma/ (568)
63 Adenomyo$.tw. (4050)
64 fibroma.tw. (6088)
65 fibromyoma$.tw. (597)
66 exp female infertility/ (37958)
67 endometriosis/ (28638)
68 exp uterus disease/ (204087)
69 exp endometrium tumor/ (46314)
70 polyp/ or endometrium polyp/ (17532)
71 endometrium hyperplasia/ (6235)
72 Endometrial Hyperplasia.tw. (3390)
73 exp ovary disease/ (158592)

74 (ovar$ adj2 mass$).tw. (2718)
75 (ovar$ adj2 tumo?r).tw. (8093)
76 uter$ cavit$.tw. (4628)
77 intracavity lesion$.tw. (7)
78 (postmenopaus$ adj2 bleed$).tw. (1464)
79 (perimenopaus$ adj2 bleed$).tw. (88)
80 (uter$ adj2 volume).tw. (1038)
81 (ovar$ adj2 volume$).tw. (1337)
82 gyn?ecology.tw. (39192)
83 or/1-82 (736804)
84 three dimensional imaging/ (68484)
85 limit 84 to yr="1990 -Current" (68477)
86 (Three-Dimensional adj2 imag$).tw. (8841)
87 (3 D adj2 imag$).tw. (2326)
88 (Three-Dimensional adj2 sonogra$).tw. (448)
89 (3D adj2 sonogra$).tw. (447)
90 (3 D adj2 sonogra$).tw. (46)
91 3dus.tw. (222)
92 3 dus.tw. (19)
93 (Three-Dimensional adj2 ultraso$).tw. (2938)
94 (3D adj2 ultraso$).tw. (2977)
95 3D US.tw. (564)
96 (3d adj2 multiplanar).tw. (221)
97 (3 dimension$ adj2 multiplanar).tw. (32)
98 (three dimension$ adj2 multiplanar).tw. (214)
99 or/85-98 (76270)
100 (Three-Dimensional and sonohysterogra$).tw. (56)
101 (3D and sonohysterogra$).tw. (60)
102 (3 D and sonohysterogra$).tw. (9)
103 (Three-Dimensional and SIS).tw. (74)
104 (3D adj2 SIS).tw. (16)
105 (3 D and SIS).tw. (9)
106 (Three-Dimensional adj2 hystero$).tw. (35)
107 (3D adj2 hystero$).tw. (37)
108 (3 D and hystero$).tw. (41)
109 (3d and hycosy).tw. (23)
110 (3 d and hycosy).tw. (2)
111 (three dimension$ and hycosy).tw. (23)
112 echography/ (248347)
113 Three dimensional.tw. (136027)
114 3dus.tw. (222)
115 3D.tw. (115055)
116 113 or 114 or 115 (219884)
117 112 and 116 (4707)
118 99 or 117 (77727)
119 83 and 118 (2423)
120 or/100-111 (257)
121 119 or 120 (2547)

7 Gynaecology and Fertility Specialised Register for RCTs

From inception until 01 March 2016

PROCITE PLATFORM

Keywords CONTAINS "3D hysterosonography"or"3D sonography"or "3D transvaginal ultrasound"or "3D ultrasound" or "three dimensional"or Title CONTAINS "3D hysterosonography"or"3D sonography"or "3D transvaginal ultrasound"or "3D ultrasound" or "three dimensional"

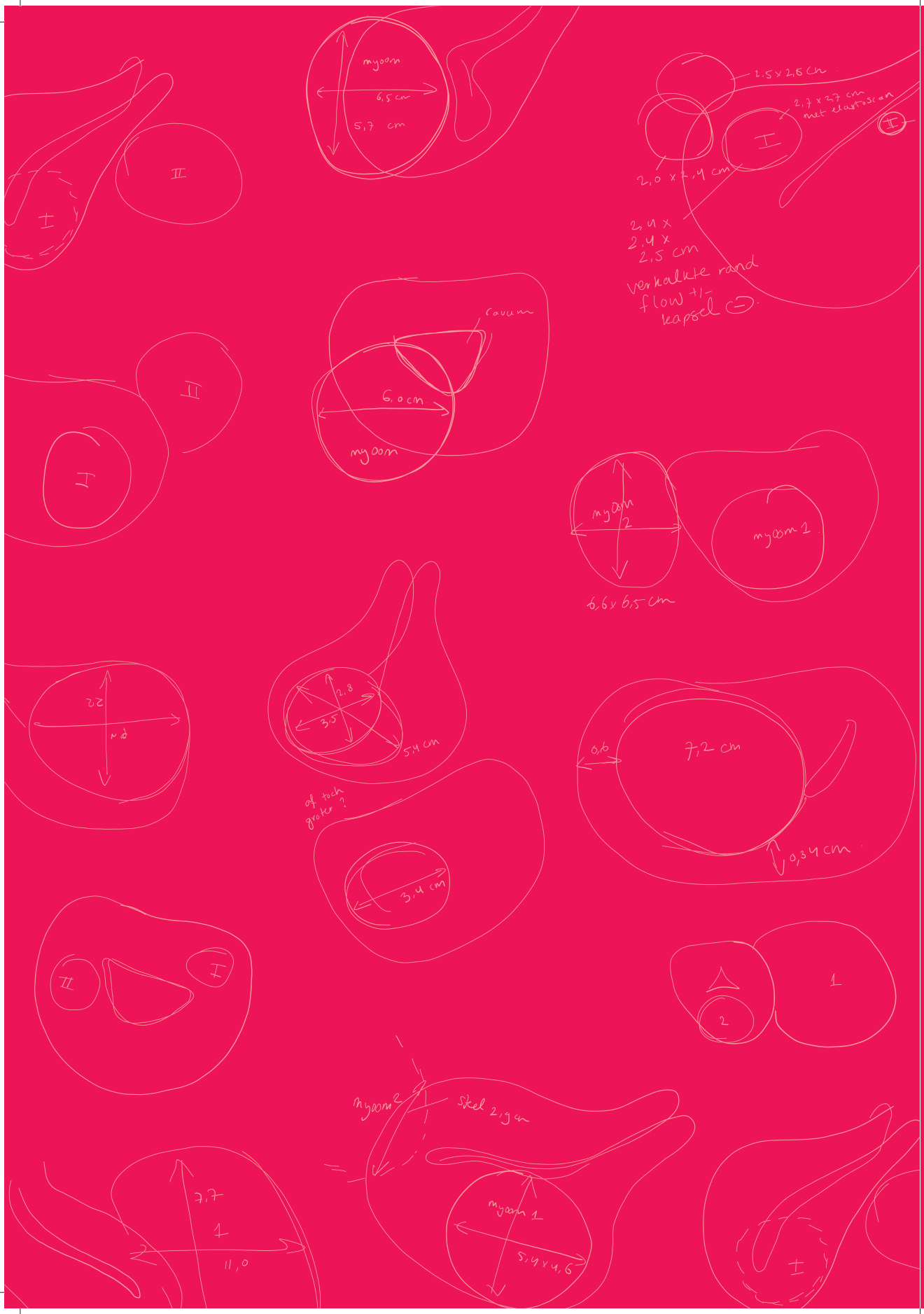
12 hits

8 Gynaecology and Fertility DTA Register

From inception until 01 March 2016
PROCITE PLATFORM

Title CONTAINS "three dimensional" or "3d" or "3 dimensional" or Keywords CONTAINS "three dimensional" or "3d" or "3 dimensional"

16 hits


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

05

The role of three-dimensional sonography in the assessment of submucous fibroids: a pilot study

A.L. Keizer
L.L. Nieuwenhuis
J.W.R. Twisk
J.A.F. Huirne
W.J.K. Hehenkamp
H.A.M. Brölmann

J Ultrasound Med. 2017 Aug 4. doi: 10.1002/jum.14331

ABSTRACT

Introduction: Fibroid protrusion into the uterine cavity is associated with the probability of successful hysteroscopic fibroid resection. Two- and three-dimensional saline infusion sonography (2D-SIS and 3D-SIS) are more accurate in classifying submucous fibroids than two-dimensional transvaginal sonography (2D-TVS). However, 2D-SIS and 3D-SIS are more invasive techniques, which justifies studying three-dimensional transvaginal sonography (3D-TVS) as potential replacement.

Objectives: To investigate the accuracy and reliability of 3D-TVS in classifying submucous fibroids using FIGO PALM-COEIN classification and protrusion (%) compared to 2D-TVS, 2D-SIS and 3D-SIS, using hysteroscopy as a reference test.

Methods: A prospective cohort (pilot) study was performed among 14 consecutive patients undergoing hysteroscopic surgery, preceded by routine ultrasonography (2D-TVS, 2D-SIS, 3D-TVS, 3D-SIS).

Results: The ICC of 2D-TVS vs. hysteroscopy is 0.69 (95% CI 0.06 – 0.90) compared to 0.94 (95% CI 0.83 – 0.98) for 2D-SIS. The ICC of 3D-TVS vs. hysteroscopy is 0.69 (95% CI 0.03 – 0.90) (investigator A) and 0.55 (95% CI -0.48 – 0.86) (investigator B). The ICC of 3D-SIS vs. hysteroscopy is 0.94 (95% CI 0.81 – 0.98) (investigator A) and 0.87 (95% CI 0.60 – 0.96) (investigator B). Inter-observer agreement of 3D-TVS is 0.81 (95% CI 0.43 – 0.94) compared to 0.86 (95% CI 0.56 – 0.96) for 3D-SIS.

Conclusions: In these preliminary data 3D-TVS is not as accurate as 2D-SIS or 3D-SIS, and 3D-TVS is not more accurate than 2D-TVS. There is a moderate interobserver agreement for 3D-TVS. There might be room for improvement, as 3D-TVS is more accurate when endometrial thickness increases. Further study is warranted to evaluate in which patients SIS eventually can be obviated.

Key words: three-dimensional, sonography, submucous, uterine fibroid, protrusion, classification

INTRODUCTION

Uterine fibroids are benign monoclonal tumors arising from smooth muscle cells of the uterus, with a reported prevalence as high as 77% [1]. Uterine fibroids are symptomatic in up to 50% of affected women, with submucous fibroids being the most common cause of heavy menstrual bleeding occurring in 30% of symptomatic women [2-4]. Fibroids can be classified according to their location in the uterus, using the FIGO PALM-COEIN classification [5]. Submucous fibroids are then subdivided into type 0 (completely intracavitary), type 1 (>50% intracavitary) and type 2 (≤50% intracavitary). In hysteroscopic treatment of submucous fibroids, higher success rates are achieved for fibroids with greater intracavitary protrusion [6]. Correct classification of submucous fibroids allows women and their gynecologists to make optimal therapeutic decisions regarding medical or surgical management.

Classification of submucous fibroids can be accomplished by transvaginal ultrasonography. Using real-time, two dimensional transvaginal ultrasonography (2D-TVS), protrusion can easily be under- or overestimated by viewing uterine cavity and fibroid in an incorrect plane. With three dimensional transvaginal ultrasonography (3D-TVS) this problem can be overcome if using a standardized measurement protocol [2;7]. Both 2D-TVS and 3D-TVS can be combined with saline infusion sonography (SIS) to improve the contrast between myometrium, fibroid and uterine cavity, however this is a more invasive procedure and can be experienced as painful [8]. Furthermore, SIS cannot be executed during the luteal cycle phase in fertile women without previous use of contraceptive methods. In current literature it is established that 2D-TVS is less accurate than 2D-SIS and hysteroscopy in detecting intra-uterine lesions, including classifying submucous fibroids [9-18].

In treatment of submucous fibroids, protrusion, diameter and size of the fibroid's intramural component measured with 3D-SIS are associated with the likelihood of successful fibroid resection [19]. Currently, the general "work-up" of patients with submucous fibroids consists of 2D-TVS and 2D-SIS. 3D-TVS or 3D-SIS are not incorporated in current practice. Regarding submucous fibroids, 3D-TVS has not yet been studied. Since TVS is less invasive than SIS, it is worth examining if 3D-TVS is equally accurate as 2D-SIS in classifying submucous fibroids. If so, SIS can be omitted.

We hypothesise that 3D-TVS is more accurate than 2D-TVS in classifying fibroids and just as accurate as 2D-SIS, using hysteroscopy as a reference test. The collection and analysis of these preliminary data enables a decision whether a larger diagnostic trial should be considered.

METHODS

A prospective cohort (pilot) study was performed among 15 consecutive patients undergoing hysteroscopic myomectomy (13 patients) or fibroid ablation (Sonata™) after diagnostic hysteroscopy (2 patients) from December 2014 until July 2015 at the Gynecology Department of the VU medical Center (VUmc) in Amsterdam, the Netherlands. All participating patients gave their consent. The study was approved by the ethical board of the VUmc.

Ultrasonography and hysteroscopy

All surgeries were performed under general anesthesia. Before surgery routine transvaginal sonographic evaluation of fibroids was performed to evaluate size, type and location of fibroids (Accuvix A30 and WS80A, Samsung Medison, Seoul, South Korea). Both two-dimensional (2D) imaging and storage of the three-dimensional (3D) image volumes were performed for transvaginal sonography (TVS) and saline infusion sonography (SIS). The 2D, real time sonographic evaluation and 3D volume recording were executed by one of five gynecologists performing the hysteroscopic surgery. The 3D sonographic evaluation was performed at a later time by two sonographers (ALK and HB) experienced in 3D off line analysis of sonographic volumes. All exams were performed under general anesthesia prior to hysteroscopic surgery. First, 2D sonographic evaluation using a standard transvaginal probe (5-9MHz) was performed and parameters were registered. Endometrial thickness and fibroid size were measured live on screen and type and percentage of protrusion were determined by estimation. Secondly a 3D volume of the entire uterus was recorded using a 3D transvaginal probe. After intra-uterine installation of a 0.9% solution of sodium chloride using a Goldstein sonohysterography catheter (Cook, Bloomington, USA), 2D sonographic evaluation was repeated using a standard transvaginal probe, parameters were registered and last another 3D volume of the entire uterus was recorded. Hysteroscopy was performed or supervised by one of five gynecologists, all experienced in advanced hysteroscopic resections. During hysteroscopy, uterine cavity and fibroid protrusion were observed with and without intra-uterine pressure (60-100 mmHg). Duration of the procedure and total fluid loss were registered. Performing gynecologist recorded size, type and location of fibroid for 2D-TVS, 2D-SIS and hysteroscopy, the estimated percentage of protrusion and interpretability of the performed exams, using a case report form. Interpretability was scored on a 4-point scale (1 = not interpretable, 2 = moderate, 3 = good and 4 = very good). Mean scores were calculated for each imaging modality.

Offline evaluation of 3D imaging

Offline analysis of 3D-TVS and 3D-SIS imaging was performed by two examinors (investigator A and B) using VOCAL software, Samsung 3D viewer (Samsung, Seoul, South Korea). Both investigators were blinded for prior sonograms and operative results and separately analyzed 3D-TVS as well as 3D-SIS in a multiplanar view. Data was coded and a case report form was used to register size, type, location and percentage of protrusion of fibroid on 3D-TVS and 3D-SIS, and interpretability of 3D-TVS and 3D-SIS. To determine fibroid location (and measure endometrial thickness), all 3D volumes were scanned in the sagittal plane containing a clear depiction of the endocervical canal and the uterine cavity and viewed in a standard (ROI 3D) setting. To measure size and protrusion (and subsequently determine type), the largest diameter of the fibroid is selected in the sagittal plane. The intersection point of two rotation axes (x and y) is placed in the center of the fibroid. While rotating the image on the x- or y-axis, the largest visible protrusion in case of a FIGO PALM-COEIN type 0 and 1 fibroid and the largest myometrial extension in case of type 2 fibroid can be considered as the true protrusion and extension. See figure 1. Interpretability of 2D-TVS, 2D-SIS and hysteroscopy was scored separately by performing gynecologist and interpretability of 3D-TVS and 3D-SIS was scored by both investigators performing offline analysis on a 4-point scale (1 = not interpretable, 2 = moderate, 3 = good and 4 = very good). Mean scores were calculated for each imaging modality.

Statistical analysis

All analyses were performed by ALK and JT using IBM SPSS Statistics 22.0 software package.

Main outcome parameters are the agreement of the percentage of intracavitary fibroid protrusion on 2D-TVS, 2D-SIS, 3D-TVS and 3D-SIS with hysteroscopy.

Intraclass Correlation Coefficient (ICC) and Bland-Altman plots were constructed to calculate inter-test (for 2D-TVS, 2D-SIS, 3D-TVS and 3D-SIS compared to hysteroscopy) and inter-observer agreement (for 3D-TVS and 3D-SIS). An ICC of 0.9 or higher was considered good agreement.

To make a more general comparison between the different types of sonography and hysteroscopy, also the kappa of the estimated type of fibroid (≤ or > 50% protrusion) on ultrasonography and sonohysterography was compared to the estimated type of fibroid on hysteroscopy. A kappa of 0.8 was considered good agreement.

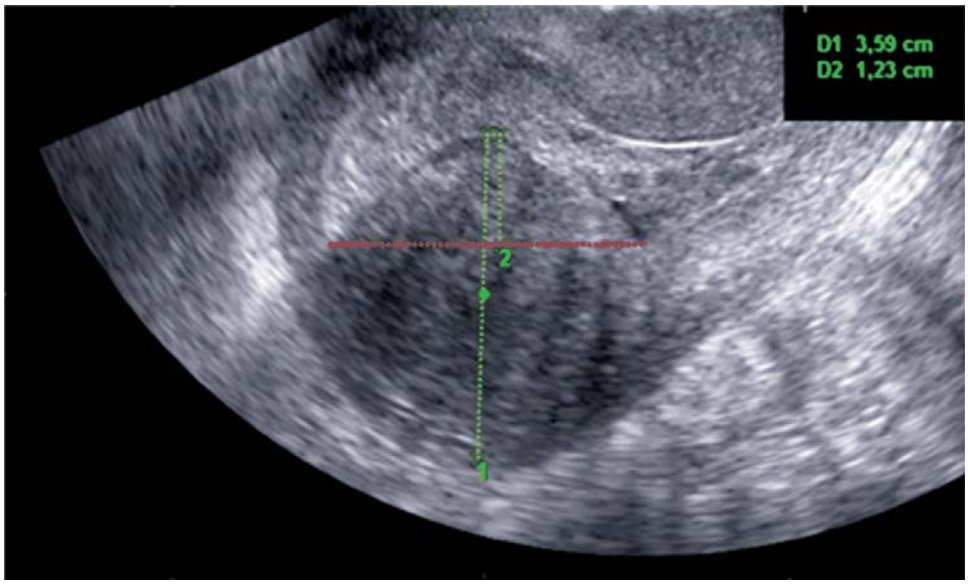


Figure 1a. Anteflected uterus on 3D-TVS without intracavitary contrast in the midsagittal plane. The endometrium and endocervical canal are hyperechogenic compared to the myometrium and fibroid. The fibroid is marked in the middle with a green dot. A 3.6 cm fibroid in the posterior uterine wall protrudes 1,23 / 3,59 * 100% = 34%, FIGO-staging the fibroid as type 2.

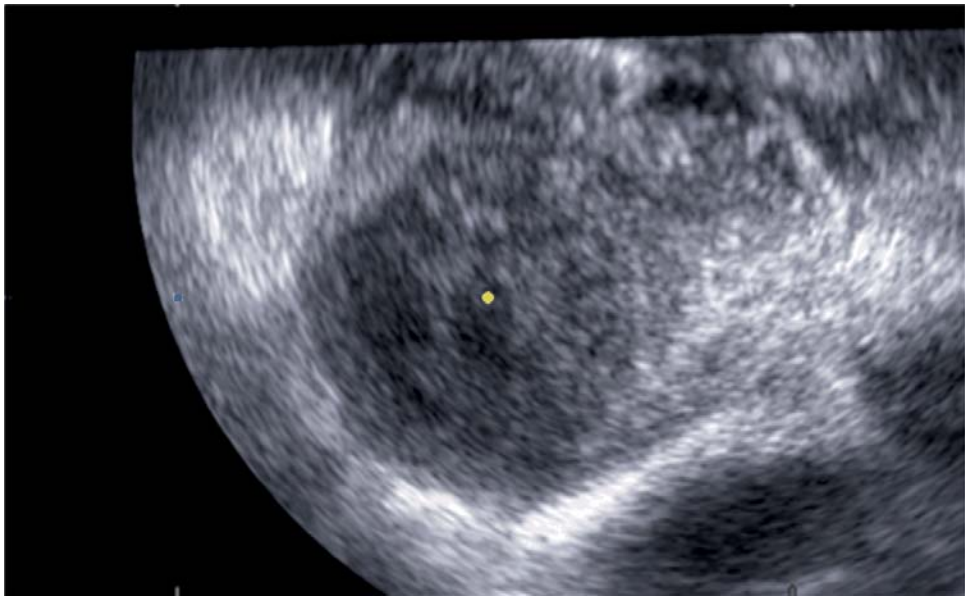


Figure 1b. After rotating the image 90° on the x-axis to the coronal plane, the fibroid is, marked in the middle with a yellow dot, completely surrounded by myometrium, indicating that the majority of the fibroid is intramural.

With the objective that low imaging quality on 3D-TVS would qualify patients to undergo 3D-SIS, uninterpretable 3D-TVS were excluded and ICC's were recalculated.

Ordinal logistic regression analyses were performed for endometrial thickness as measured on 2D-TVS (to eliminate any errors in measurement between investigator A and B) and interpretability of 3D-TVS scored on a 4-point scale by both investigator A and B.

RESULTS

Baseline characteristics

One patient was excluded due to incomplete data. Fourteen women were included, all were premenopausal, with a mean age of 42 (range 36 – 51). Oral contraceptives were used in 29% of the women. Parity ranged from 0 - 2. Presenting symptoms were abnormal uterine bleeding (85,7%), abdominal pain (7,1%) or subfertility (7,1%).

Fibroid characteristics

13 patients had 1 fibroid, 1 patient had 2 fibroids (the second fibroid was disregarded). For other fibroid characteristics see table 1.

Table 1

FIBROID CHARACTERISTICS AS MEASURED ON 2D-TVS		
Fibroid location in the uterus	Anterior	n=6
	Posterior	n=5
	Fundus	n=2
	Unknown origin	n=1
Maximum fibroid diameter	< 3 cm	n=2
	3-5 cm	n=7
	>5 cm	n=5
Fibroid type	0	n=1
	1	n=5
	2	n=8

ICC of percentage of protrusion compared to hysteroscopy

ICC's of the estimated percentages of protrusion on transvaginal ultrasonography or sonohysterography were compared to hysteroscopy as a reference. See table 2. Protrusion is estimated to be slightly larger and the angle between fibroid and myometrium is

estimated to be slightly smaller without intra-uterine pressure (results not shown). Protrusion during hysteroscopy with intra-uterine pressure of a maximum of 100 was chosen as the main reference test, because distension is indispensable in performing hysteroscopy. We also compared the results to hysteroscopy with intra-uterine pressure switched off and 3D-SIS as a reference. For accompanying Bland-Altman plots see figure 2, limits of agreement are shown as upper and lower 95% confidence interval lines on a comparable scale.

Table 2. Agreement of estimated percentage of protrusion compared to hysteroscopy (intra-uterine pressure on and off) and 3D-SIS as a reference

INDEX TEST	REFERENCE TEST	ICC (CI)*
2D-TVS	pressure on	ICC 0.69 (95% CI 0.06 – 0.90)
	pressure off	ICC 0.59 (95% CI -0.18 – 0.87)
	3D-SIS (mean)	ICC 0.67 (95% CI -0.10 – 0.90)
2D-SIS	pressure on	ICC 0.94 (95% CI 0.83 – 0.98)
	pressure off	ICC 0.91 (95% CI 0.63 – 0.98)
	3D-SIS (mean)	ICC 0.96 (95% CI 0.87 – 0.99)
3D-TVS (investigator A)	pressure on	ICC 0.69 (95% CI 0.03 – 0.90)
	pressure off	ICC 0.68 (95% CI 0.05 – 0.90)
	3D-SIS (mean)	ICC 0.70 (95% CI 0.03 – 0.90)
3D-TVS (investigator B)	pressure on	ICC 0.55 (95% CI -0.48 – 0.86)
	pressure off	ICC 0.56 (95% CI -0.48 – 0.87)
	3D-SIS (mean)	ICC 0.64 (95% CI -0.04 – 0.88)
3D-SIS (investigator A)	pressure on	ICC 0.94 (95% CI 0.81 – 0.98)
	pressure off	ICC 0.90 (95% CI 0.39 – 0.98)
3D-SIS (investigator B)	pressure on	ICC 0.87 (95% CI 0.60 – 0.96)
	pressure off	ICC 0.83 (95% CI 0.16 – 0.95)

* Intraclass Correlation Coëfficient (confidence interval)

Inter-observer agreement 3D-TVS and 3D-SIS

Inter-observer agreement of 3D-TVS has an ICC of 0.81 (95% CI 0.43 – 0.94). Inter-observer agreement of 3D-SIS has an ICC of 0.86 (95% CI 0.56 – 0.96). Because both ICC values are within the confidence interval of the other we can conclude that there is no significant difference between the ICC values of both methods. For accompanying Bland-Altman plots see figure 3, limits of agreement are shown as upper and lower 95% confidence interval lines on a comparable scale.

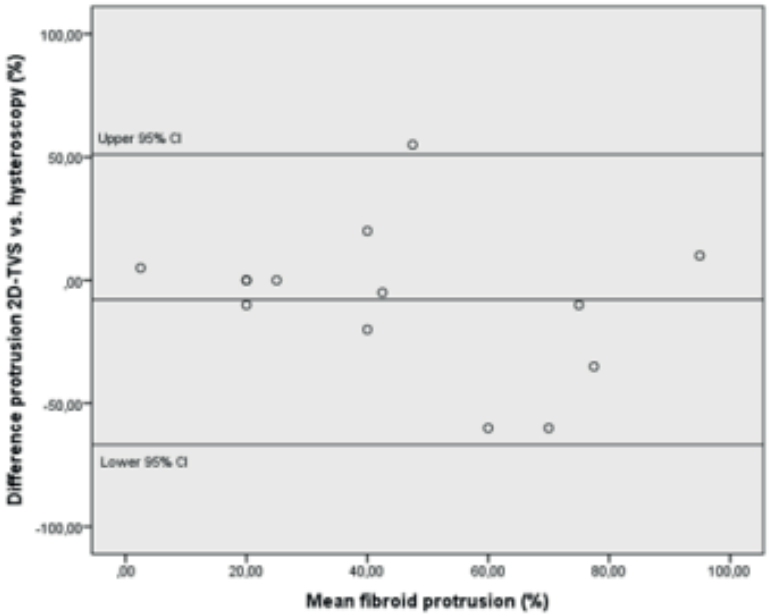


Figure 2a. Bland-Altman plot of 2D-TVS vs. hysteroscopy.

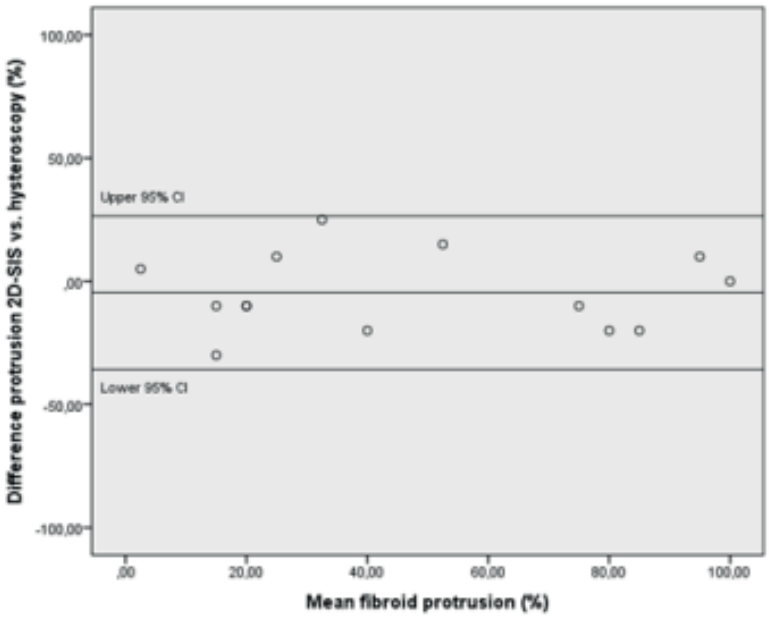


Figure 2b. Bland-Altman plot of 2D-SIS vs. hysteroscopy.

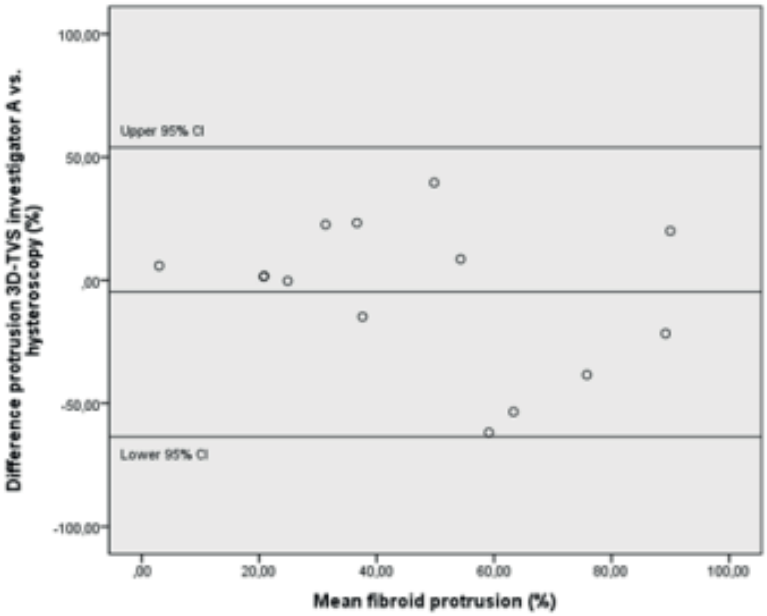


Figure 2c. Bland-Altman plot of 3D-TVS (investigator A) vs. hysteroscopy.

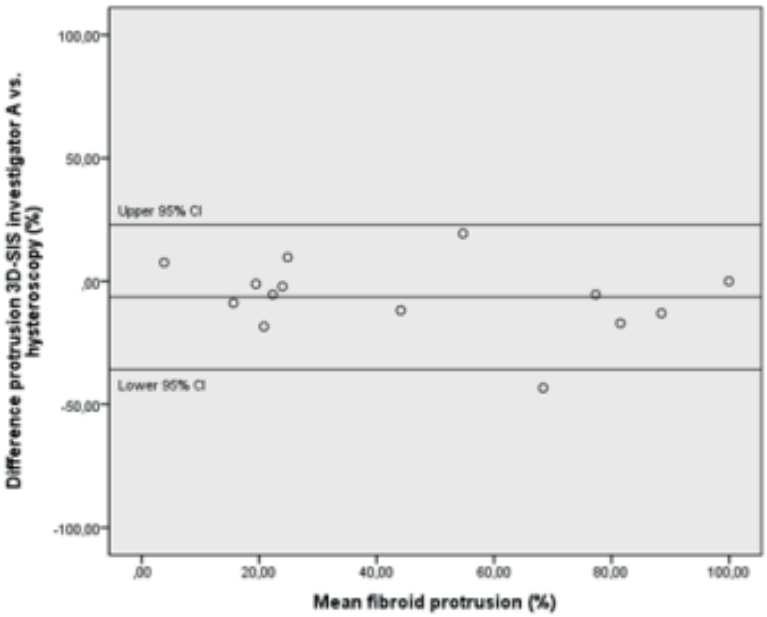


Figure 2d. Bland-Altman plot of 3D-SIS (investigator A) vs. hysteroscopy.

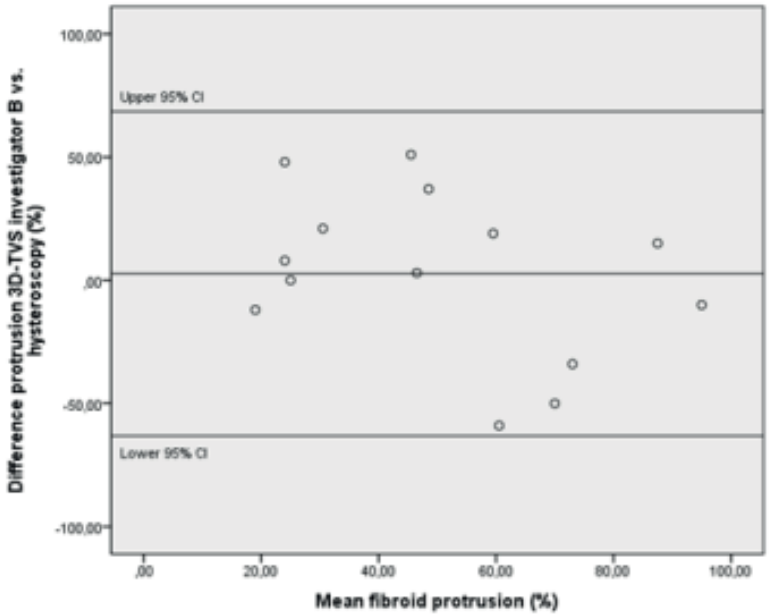


Figure 2e. Bland-Altman plot of 3D-TVS (investigator B) vs. hysteroscopy.

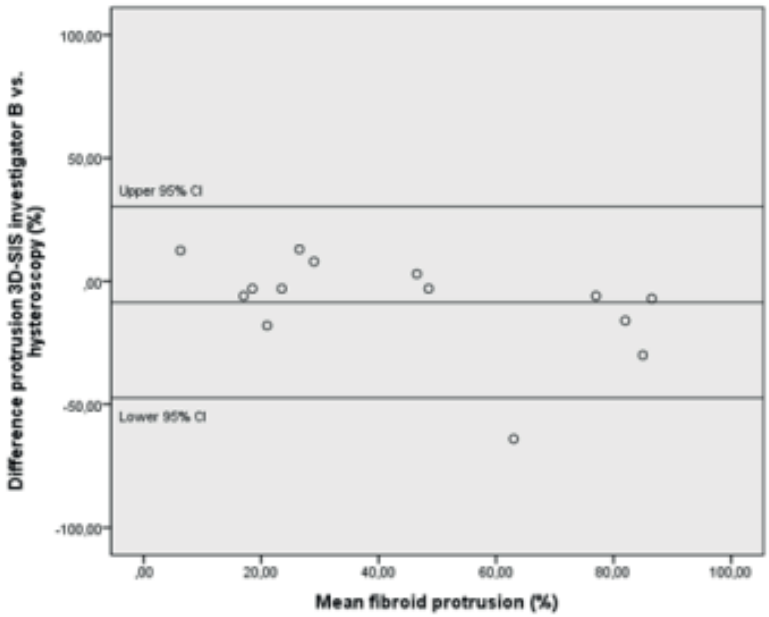


Figure 2f. Bland-Altman plot of 3D-SIS (investigator B) vs. hysteroscopy.

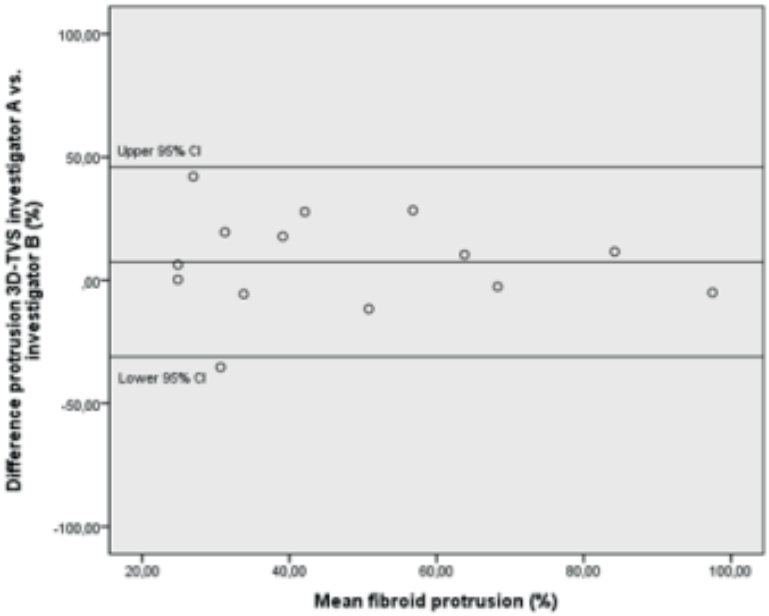


Figure 3a. Bland-Altman plot of the interobserver agreement of 3D-TVS.

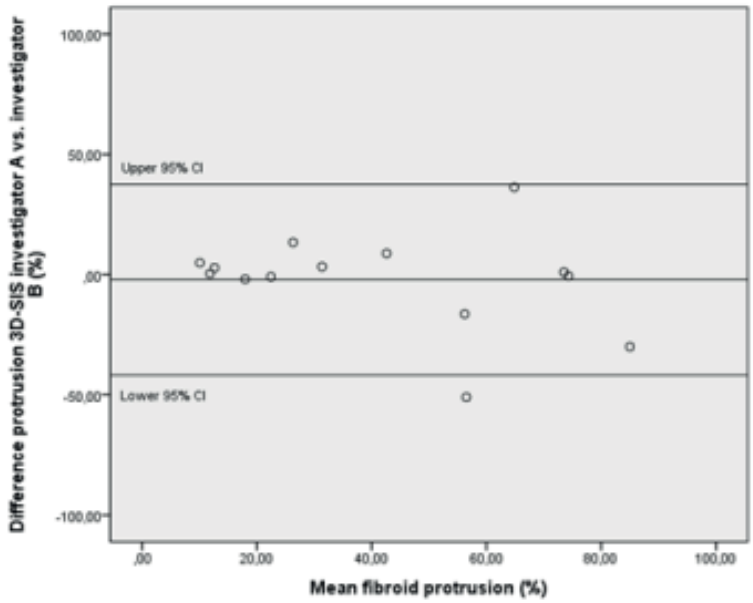


Figure 3b. Bland-Altman plot of the interobserver agreement of 3D-SIS.

Kappa of FIGO fibroid classification with hysteroscopy as reference

2D-TVS has a kappa of 0.55. 2D-SIS has a kappa of 0.85. 3D-TVS has a kappa of 0.51 (investigator A) and 0.26 (investigator B). 3D-SIS has a kappa of 0.69 (investigator A) and 0.84 (investigator B). Results are comparable to ICC of percentage of protrusion (see table 1), which was scored slightly better.

Inter-observer agreement 3D-TVS and interpretability

Interpretability was scored on a 4-point scale (1 = not interpretable, 2 = moderate, 3 = good and 4 = very good). See table 3. Excluding uninterpretable and moderately interpretable 3D-TVS as scored by at least one of the investigators (n=8) did not improve the interobserver agreement (results not shown). Interpretability of 3D-TVS seems to be better with increasing endometrial thickness (OR 1.34 95% CI 0.80 – 2.26 p=0.272 for investigator A, OR 1.27 95% CI 0.76 – 2.13 p=0.361 for investigator B), although results are not statistically significant.

Table 3. Interpretability

IMAGING MODALITY	MEAN SCORE
2D-TVS	3,000 (SD 0,5547)
2D-SIS	3,538 (SD 0,7763)
3D-TVS A	3,000 (SD 0,7845)
3D-TVS B	2,790 (SD 0,8020)
3D-SIS A	3,286 (SD 0,7263)
3D-SIS B	3,357 (SD 0,9288)
Hysteroscopy	3,540 (SD 0,6600)

(1 = not interpretable, 2 = moderate, 3 = good and 4 = very good)

Under- and overestimation of protrusion

Protrusion scored using 3D-TVS by investigator A and B showed approximately half of the protrusions are estimated correctly (a maximum of 20% less or more protrusion than on hysteroscopy), a quarter is underestimated and a quarter is overestimated. See table 4. For investigator A, 50% of the overestimated protrusions (2 out of 4) and

75% (3 out of 4) of the underestimated protrusions led to an adjustment in fibroid type. For investigator B, 75% of the overestimated protrusions (3 out of 4) and 66% of the underestimated protrusions (2 out of 3) led to an adjustment in fibroid type.

Table 4. Under- and overestimation of protrusion on 3D-TVS (protrusion transformed to a 3-point ordinal scale, for correct estimation a difference ± 20% compared to hysteroscopy (pressure on) was accepted)

	PERCENTAGE	MEAN ENDOMETRIAL THICKNESS (MM)	MEAN PROTRUSION ON HYSTEROSCOPY (%)
	Investigator A		
Underestimated	28.6%	3.73 (SD 1.05)	93.75 (SD 4.79)
Overestimated	28.6%	4.13 (SD 1.98)	38.75 (SD 27.80)
Correct estimation	42.9%	5.62 (SD 2.40)	26.67 (SD 18.35)
	Investigator B		
Underestimated	21.4%	3.63 (SD 1.27)	91.76 (SD 2.89)
Overestimated	28.6%	5.53 (SD 2.93)	17.50 (SD 12.58)
Correct estimation	50.0%	4.59 (SD 1.77)	49.29 (SD 30.47)

DISCUSSION

Main findings

3D-TVS is equivalent to 2D-TVS, but not as accurate as 2D-SIS or 3D-SIS in estimating the percentage of protrusion, compared to hysteroscopy. Correct estimation (± 20%) is achieved in half of the fibroids only using 3D TVS, but this improves with increasing endometrial thickness. Interobserver agreement for 3D-TVS is moderate and seems to be better with a greater percentage of fibroid protruding into the uterine cavity. Interobserver agreement of 3D-SIS is good and seems slightly better for smaller portions of fibroid protruding into the uterine cavity.

Strengths and limitations

No previous studies investigating the agreement of 2D-TVS, 2D-SIS, 3D-TVS and 3D-SIS with hysteroscopy simultaneously have been reported. The obvious limitation of this pilot study is the small number of patients. As this study was set up as a pilot study, the sample size was not powered to detect significant differences. The hysteroscopic surgeon

was not blinded for (previous) 2D-TVS and 2D-SIS results. In preparing for surgery, the surgeon had access to the patient's medical record, including descriptions and pictures of previous ultrasounds and additionally the surgeon performing hysteroscopy also performed the 2D-TVS and 2D-SIS beforehand. This could have caused bias in scoring the protrusion during hysteroscopy and the agreement of 2D-TVS and 2D-SIS with hysteroscopy could therefore have been overestimated. Investigators performing offline analysis of coded 3D-sweeps were blinded for previous results, however 3D-TVS and 3D-SIS of the same patient were reviewed in a consecutive manner. Interobserver agreement was only tested for 3D-TVS and 3D-SIS, for which both offline examiners analyzed all patients. Interobserver agreement was not investigated for 2D-TVS or 2D-SIS. Since these techniques are standard practice, they are assumed to have a low interobserver variability and due to the high number of investigators (5), the limited number of patients (14) in this pilot study, investigation of the interobserver agreement for 2D-TVS and 2D-SIS was deamed not feasible. However, this should be a point of focus for future research. Interpretability seems to be better with increasing endometrial thickness, however results are not statistically significant, most likely due to the small study population.

Comparison with available literature

In this pilot study 3D-TVS is equivalent to 2D-TVS, but not as accurate as 2D-SIS or 3D-SIS in estimating the percentage of protrusion, compared to hysteroscopy. Many studies have investigated the accuracy and reliability of 3D-SIS, with comparable results to ours. 3D-SIS offers adequate visualization and characterization of intra-uterine abnormalities and is reported to be a reproducible method for the quantification of the percentage of protrusion of a submucous fibroid [2;20-25]. Unfortunately, 3D-TVS is not widely investigated.

Visual inspection of the Bland-Altman plots shows that a smaller percentage of fibroid protruding into the uterine cavity is inclined to be overestimated on 3D-TVS compared to hysteroscopy and a greater percentage of fibroid protruding into the uterine cavity is inclined to be underestimated. 3D-SIS is reported to have a better overall agreement with hysteroscopy in cases where a greater proportion of the fibroid is contained within the uterine cavity [26]. In contrast we did not find a major difference. The present study shows moderate interobserver agreement for 3D-TVS and a good interobserver agreement for 3D-SIS in measuring percentage of protrusion. This is in concordance with reported literature. In diagnosing uterine fibroids specifically, 3D-SIS interobserver and intraobserver agreement are moderate to good for fibroid protrusion into the uterine cavity [2;25]. After visual inspection of the Bland-Altman plots, interobserver agreement

of 3D-TVS seems to increase with a greater percentage of fibroid protruding into the uterine cavity and interobserver agreement of 3D-SIS seems slightly better for smaller portions of fibroid protruding into the uterine cavity.

Clinical consequences and conclusion

Concerning 3D-TVS (and to a lesser extent also 3D-SIS), visual inspection of the Bland-Altman plots shows that fibroid protrusion < 50% is generally overestimated and fibroid protrusion >50% is generally underestimated by both investigators, compared to hysteroscopy. This might be due to difficulties in distinguishing uterine cavity from fibroid capsule, especially when the endometrial lining is thin. Correct estimation seems to be easier with increasing endometrial thickness. A possible reason for overestimation of the protrusion on 3D-TVS, without saline as contrast medium, is the possible confusion between endometrial depiction, mostly more echogenic than myometrium or fibroid, and the intramural pseudocapsula of the fibroid which also appears as a hyperechogenic line. Another reason might be the difference between inclusion of endometrium in the protrusion on 3D-TVS, especially when it is thick, and exclusion of the endometrium in the protrusion in case of 3D SIS. Finally the effect of distension of the uterine cavity, which is not applied in 3D-TVS, on fibroid protrusion is not well known. The protrusion may increase while there is no distending counterforce but protrusion may also decrease without low resistance distention of the cavity. In case of underestimation of the protrusion on 3D-TVS, the endometrium is not identified properly because of low thickness or ultrasound artifacts such as shadowing. Overestimation of the protrusion could theoretically lead to a more complicated fibroid resection. Taking the above into account, there might be room for improvement, especially in overestimation of the protrusion. In case of thin endometrium an adequate evaluation of the cavity becomes problematic and a SIS should be considered.

The current preliminary data do not allow firm conclusions on the accuracy of 3D-TVS to classify submucous fibroids. 2D-SIS or 3D-SIS, as well as hysteroscopy, remain the gold standard in assessing fibroid protrusion. A larger scale study is needed to draw more definite conclusions, using the data of this pilot study to refine diagnostic criteria and protocol, possibly making SIS redundant in a substantial number of patients in the future.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990 Oct;94(4):435-8.
2. Lee C, Salim R, Ofili-Yebovi D, Yazbek J, Davies A, Jurkovic D. Reproducibility of the measurement of submucous fibroid protrusion into the uterine cavity using three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol 2006 Nov;28(6):837-41.
3. Stovall DW. Clinical symptomatology of uterine leiomyomas. Clin Obstet Gynecol 2001 Jun;44(2):364-71.
4. Gupta S, Jose J, Manyonda I. Clinical presentation of fibroids. Best Pract Res Clin Obstet Gynaecol 2008 Aug;22(4):615-26.
5. Munro MG, Critchley HO, Fraser IS. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertil Steril 2011 Jun;95(7):2204-8, 2208.
6. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol 1993 Nov;82(5):736-40.
7. Leone FP, Bignardi T, Marciante C, Ferrazzi E. Sonohysterography in the preoperative grading of submucous myomas: considerations on three-dimensional methodology. Ultrasound Obstet Gynecol 2007 Jun;29(6):717-8.
8. Van den Bosch T, Betsas G, Van SD, Daemen A, Vandenbroucke V, Cornelis A, et al. Gel infusion sonography in the evaluation of the uterine cavity. Ultrasound Obstet Gynecol 2009 Dec;34(6):711-4.
9. de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG 2003 Oct;110(10):938-47.
10. Alborzi S, Parsanezhad ME, Mahmoodian N, Alborzi S, Alborzi M. Sonohysterography versus transvaginal sonography for screening of patients with abnormal uterine bleeding. Int J Gynaecol Obstet 2007 Jan;96(1):20-3.
11. Becker E Jr, Lev-Toaff AS, Kaufman EP, Halpern EJ, Edelweiss MI, Kurtz AB. The added value of transvaginal sonohysterography over transvaginal sonography alone in women with known or suspected leiomyoma. J Ultrasound Med 2002 Mar;21(3):237-47.
12. Dueholm M, Forman A, Jensen ML, Laursen H, Kracht P. Transvaginal sonography combined with saline contrast sonohysterography in evaluating the uterine cavity in premenopausal patients with abnormal uterine bleeding. Ultrasound Obstet Gynecol 2001 Jul;18(1):54-61.
13. Bingol B, Gunenc Z, Gedikbasi A, Guner H, Tasdemir S, Tiras B. Comparison of diagnostic accuracy of saline infusion sonohysterography, transvaginal sonography and hysteroscopy. J Obstet Gynaecol 2011;31(1):54-8.

14. Nanda S, Chadha N, Sen J, Sangwan K. Transvaginal sonography and saline infusion sonohysterography in the evaluation of abnormal uterine bleeding. Aust N Z J Obstet Gynaecol 2002 Nov;42(5):530-4.

15. Nass DM, Oz U, Ozer C, Yildiz A, Apaydin FD, Cil F. Diagnostic value of sonohysterography in the evaluation of submucosal fibroids and endometrial polyps. Aust N Z J Obstet Gynaecol 2003 Dec;43(6):448-52.

16. Dijkhuizen FP, De Vries LD, Mol BW, Brolmann HA, Peters HM, Moret E, et al. Comparison of transvaginal ultrasonography and saline infusion sonography for the detection of intracavitary abnormalities in premenopausal women. Ultrasound Obstet Gynecol 2000 May;15(5):372-6.

17. Leone FP, Lanzani C, Ferrazzi E. Use of strict sonohysterographic methods for preoperative assessment of submucous myomas. Fertil Steril 2003 Apr;79(4):998-1002.

18. Sylvestre C, Child TJ, Tulandi T, Tan SL. A prospective study to evaluate the efficacy of two- and three-dimensional sonohysterography in women with intrauterine lesions. Fertil Steril 2003 May;79(5):1222-5.

19. Mavrelos D, Naftalin J, Hoo W, Ben-Nagi J, Holland T, Jurkovic D. Preoperative assessment of submucous fibroids by three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol 2011 Sep;38(3):350-4.

20. Ayoubi JM, Fanchin R, Ferretti G, Pons JC, Bricault I. Three-dimensional ultrasonographic reconstruction of the uterine cavity: toward virtual hysteroscopy? Eur Radiol 2002 Aug;12(8):2030-3.

21. Van den Bosch T, Valentin L, Van SD, Luts J, Bignardi T, Condous G, et al. Detection of intracavitary uterine pathology using offline analysis of three-dimensional ultrasound volumes: interobserver agreement and diagnostic accuracy. Ultrasound Obstet Gynecol 2012 Oct;40(4):459-63.

22. de Kroon CD, Louwe LA, Trimbos JB, Jansen FW. The clinical value of 3-dimensional saline infusion sonography in addition to 2-dimensional saline infusion sonography in women with abnormal uterine bleeding: work in progress. J Ultrasound Med 2004 Nov;23(11):1433-40.

23. Makris N, Skartados N, Kalmantis K, Mantzaris G, Papadimitriou A, Antsaklis A. Evaluation of abnormal uterine bleeding by transvaginal 3-D hysterosonography and diagnostic hysteroscopy. Eur J Gynaecol Oncol 2007;28(1):39-42.

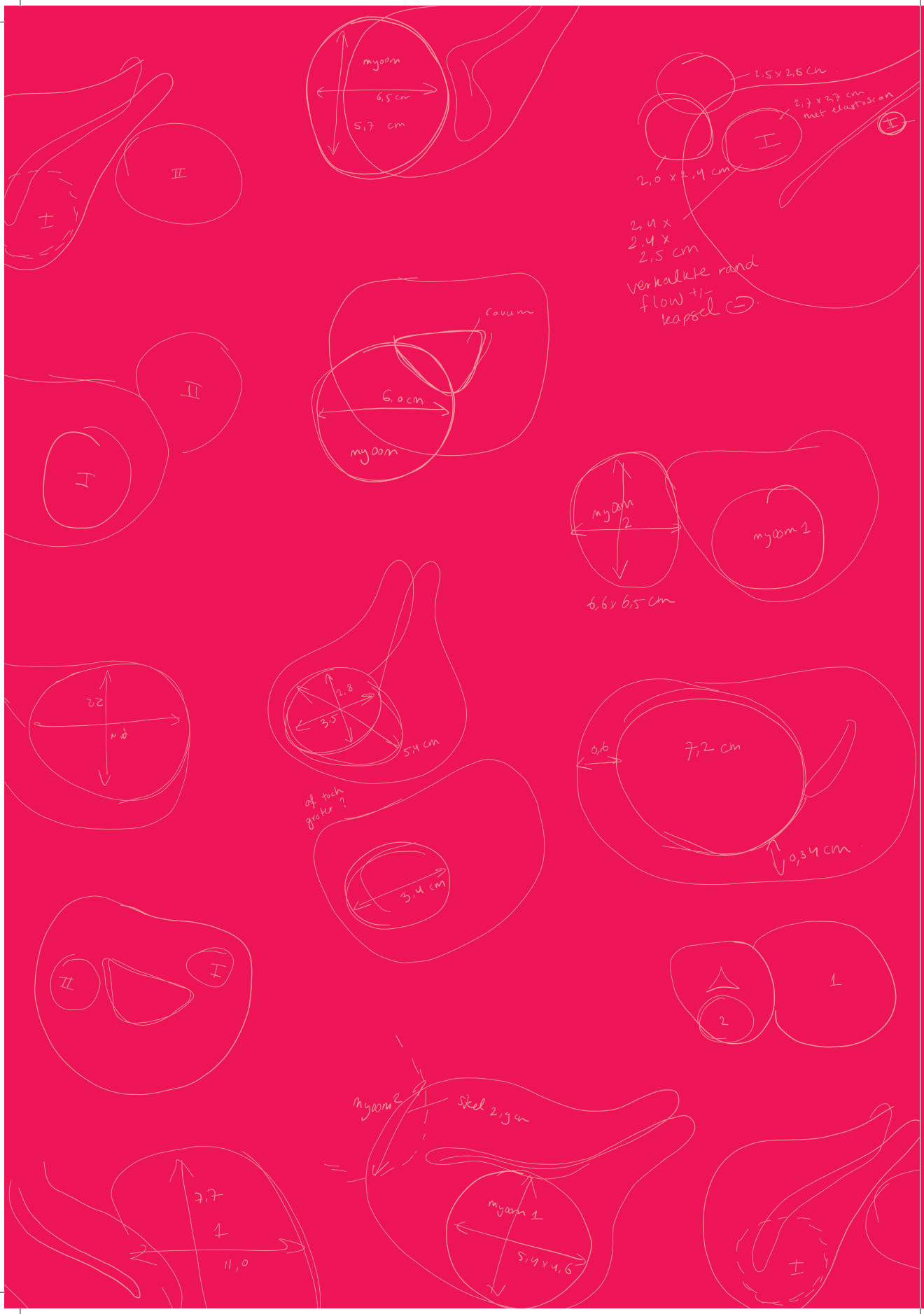
24. Nieuwenhuis LL, de Vaate MA, Hehenkamp WJ, Heymans MW, van Baal MW, Brolmann HA, et al. Diagnostic and clinical value of 3D gel installation sonohysterography in addition to 2D gel installation sonohysterography in the assessment of intrauterine abnormalities. Eur J Obstet Gynecol Reprod Biol 2014 Apr;175:67-74.

25. Nieuwenhuis LL, Bij de Vaate MA, Hehenkamp WJ, Heymans MW, van Baal MW, Brolmann HA, et al. Reproducibility of three-dimensional gel installation sonohysterography in the assessment and classification of intrauterine abnormalities. Eur J Obstet Gynecol Reprod Biol 2014 Aug;179:141-6.

26. Salim R, Lee C, Davies A, Jolaoso B, Ofuasia E, Jurkovic D. A comparative study of three-dimensional saline infusion sonohysterography and diagnostic hysteroscopy for the classification of submucous fibroids. Hum Reprod 2005 Jan;20(1):253-7.

PART II

Imaging of uterine fibroids


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

06

The use of 3D power Doppler ultrasound in the quantification of blood vessels in uterine fibroids: feasibility and reproducibility

Lotte L. Nieuwenhuis
Heleen E. Betjes
Wouter J.K. Hehenkamp
Martijn W. Heymans PhD
Prof. Hans A.M. Brolmann
Judith A.F. Huirne

J Clin Ultrasound. 2014 Aug 11. doi: 10.1002/jcu.22208

ABSTRACT

Purpose: To evaluate the interobserver agreement and discriminating value of three-dimensional Power Doppler ultrasound (3D PDUS) in patients with fibroids.

Methods: An observational prospective cohort study in 19 patients with fibroids. 3D PDUS was performed by one examiner and evaluated by three independent examiners in order to evaluate various vascular parameters: Vascular Index (VI), Flow Index (FI) and Vascular Flow Index (VFI) of the fibroid, the vascular capsule and of its highest vascular area, using both manual and automatic contour modes. The intraclass correlation coefficient and discriminating values were calculated. The correlation between VI and volume was studied using Kendall's Tau test.

Results: in the manual contour mode, the VI of the fibroid and of the vascular capsule had the highest interobserver agreement (ICC 0.89 and 0.87, respectively). Both parameters seem to have good discriminating values, given the large range of these parameters between different fibroids, independent of their volume. The vascularity of the fibroid and capsule were related. VI was not related to the volume of the fibroid.

Conclusion: VI assessed using 3D PDUS is a reproducible parameter in the assessment of fibroid vascularisation with discriminating abilities. Additional studies are needed to further evaluate validity and its clinical relevance.

Keywords: Fibroid, Leiomyoma, 3D Power Doppler, Vascularity, Reproducibility

INTRODUCTION

Submucosal fibroids are the most important cause of bleeding disorders in premenopausal women. Population studies reveal that 21 to 48% of white women have fibroids [1] for black women this number is even higher and symptoms are more severe and start at a younger age [2]. Most of these women have significant bleeding disorders that have negative effects on health-related quality of life [3;4]. Minimally invasive therapies, such as uterine artery embolisation (UAE), MRI-guided high-intensity focussed ultrasound (HIFU), laparoscopic occlusion of uterine arteries and myolysis, are emerging alternatives for radical surgery such as hysterectomy. UAE targets the fibroid by occluding the vessels of the uterus and/or the fibroid itself, aiming at ischemic infarction of the fibroid. Failure rates resulting in hysterectomies vary between 23.5% within two years [5] and up to 28.4% after a follow-up of 5 years [6]. MR-guided focussed ultrasound (MRgFUS) utilizes focussed ultrasound waves to generate high temperatures within the fibroid, resulting in coagulative necrosis. After a follow-up of 24 months, re-intervention rate is 14 to 22%[7]. Vascularity of fibroids may play a role in the effectiveness of these minimal invasive techniques. MRI-based vascularity of the targeted fibroids is correlated with the success rate of the UAE [8], while MRgFUS is reported to be less suitable for fibroids with a high vascularity, which is related to a lower volume reduction [9;10]. Vascularity was evaluated in these studies using dynamic MRI with intravenous contrast, which is an expensive and time-consuming procedure. Recently, 3D Power Doppler (3D PDUS) has become available, in theory allowing the quantification of uterine vascularity. However, exact information on its clinical relevance and its additional value to normal 2D greyscale US with MRI or histology as reference tests are lacking. In addition, to our knowledge no previous studies have been performed to study reproducibility of 3D PDUS vascular parameters of fibroids. Up to now, one prospective cohort study reported a positive correlation between 3D PDUS parameters (VI and VFI) and histopathological vascular parameters in fibroids [11]. The aim of this study is to identify vascular parameters in the assessment of fibroids and to evaluate their reproducibility.

METHODS

Study design

Between January 2012 and March 2012, 3D volumes from patients with fibroids were analysed at the department of obstetrics and gynaecology of the VU medical centre, Amsterdam (university referral centre for women with uterine fibroids). Included consecutively were premenopausal women, older than 18 years with at least one fibroid that could be visualised properly on conventional greyscale 2D US using a vaginal

probe. The study was exempt from approval by the ethical board as transvaginal US is considered regular care. Exclusion criteria were the inability to perform a transvaginal US, suspicion of uterine or cervical malignancy, pregnancy or adenomyosis.

Ultrasound

All women underwent a transvaginal real-time 2D greyscale US followed by a 3D Power Doppler (3D PDUS) on the day of their visit using the Accuvix XQ ultrasound machine (Samsung, Seoul, South Korea) with the same settings on the 3D 5-8 EK (5-8 MHz) vaginal probe. All volumes were acquired by an experienced examiner (HBR) in a standardised way. First a 2D B-mode real-time US of the uterus and ovaries was performed. The following features of the target fibroid were recorded: position in the uterus, classification, shape, size and echotexture (low, equal or high echogenicity in comparison to normal myometrium). The Power Doppler mode was activated and the 3D region of interest sector was manually adjusted to contain the entire fibroid. Power Doppler settings were set to achieve maximum sensitivity for detecting low-velocity flow without noise; frequency 5-8 MHz, Gain 50 dB (scale 0-100), pulse repetition frequency 0.60 kHz, Wall motion filter low 0 (scale 0-3). Women were asked to lie as still as possible while the 3D volume was acquired using a sweep of 60 to 90 degrees, dependent on the size of the fibroid. All acquired volume datasets were digitally stored on a personal computer as mvl and VOO files.

Evaluation of the 3D Volume datasets

Where women had multiple fibroids, the largest fibroid that could be visualised was studied (target fibroid). A subjective impression of the vascularity of the fibroid, its (pseudo) capsule and centre of the fibroid were scored (by one observer) on a Likert scale of 1 to 5, with 1 being not vascularised and 5 being very well vascularised. All stored volume datasets were evaluated using VOCAL software, Sonoview Pro- 1.5 (Samsung Medison, Seoul, South Korea) by three independent examiners (HBR, WHE, HBE). This is a rotational technique of volume calculation in which the dataset is rotated through 180⍟ around a central axis defined by the application of two callipers [12].

We used the 30⍟ rotation step (6 different planes), with the fibroid contours being outlined using both the manual and automatic sphere modes according to a standardised protocol. Volume and vascular parameters (indices) were measured for the fibroid, its capsule and centre of the fibroid (figure 1). The main contour axis was positioned in the centre of the fibroid and the poles were set at the boundaries of the fibroid. The manual contour mode was applied to outline the shape of the entire fibroid. The contour was automatically copied to the next image plane and redefined

if necessary (figure 2a). In the automatic contour mode, the poles were placed at the boundaries of the fibroid, and a round shape (sphere) was automatically selected (figure 2b). In order to study the capsule of the fibroid, a shell contour mode was applied. The pseudo or vascular capsule is an anatomically distinct structure surrounding the fibroid and has its own gene expression profile [13] and rich vascular network [14;15]. The pseudo capsule can be visualised using colour Doppler US or PDUS as a ring-shaped vascular network around the fibroid. The shell contour used consists of an inner outline and an outer outline at the border of the fibroid with a total thickness of 0.5 cm (figure 3). The centre was defined as the fibroid minus the inner shell. The vascular parameters of the fibroid, the capsule and the centre of the fibroid were automatically calculated in the histogram function of the VOCAL software. Finally, a 2 cm^3 volume sample (automatic sphere mode) was taken from the part with the highest subjectively estimated vessel concentration in the fibroid (excluding the vascular capsule of the fibroid) defined as the "highest vascular area" (HVA) [12].

Vascular assessment was based on various 3D vascular parameters: Vascularity Index (VI), Flow Index (FI) and Vascularity Flow Index (VFI) (figure 4). The VI is the number of colour voxels divided by the total number of both colour and grey voxels, representing the proportion of blood vessels within the tissue. The FI is the average colour value of all colour voxels, indicating the average flow velocity. The VFI is the average colour value of all grey and colour voxels within the volume, a product of the VI and the FI.

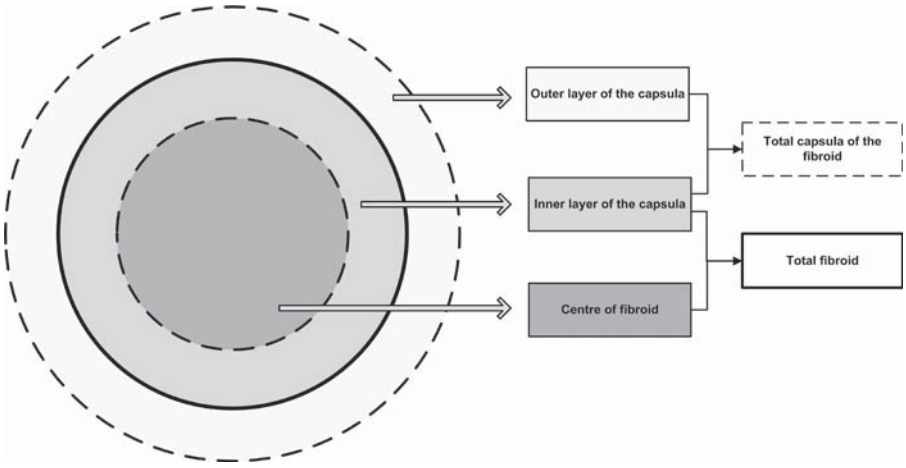


Figure 1. Schematic view of different fibroid outlines used for the measurement of fibroid volume and vascular parameters. Volumes of the fibroid and shell of the fibroid can be obtained with both manual and automatic contour mode. The shell contour mode was used to measure the vascularity of the capsule.

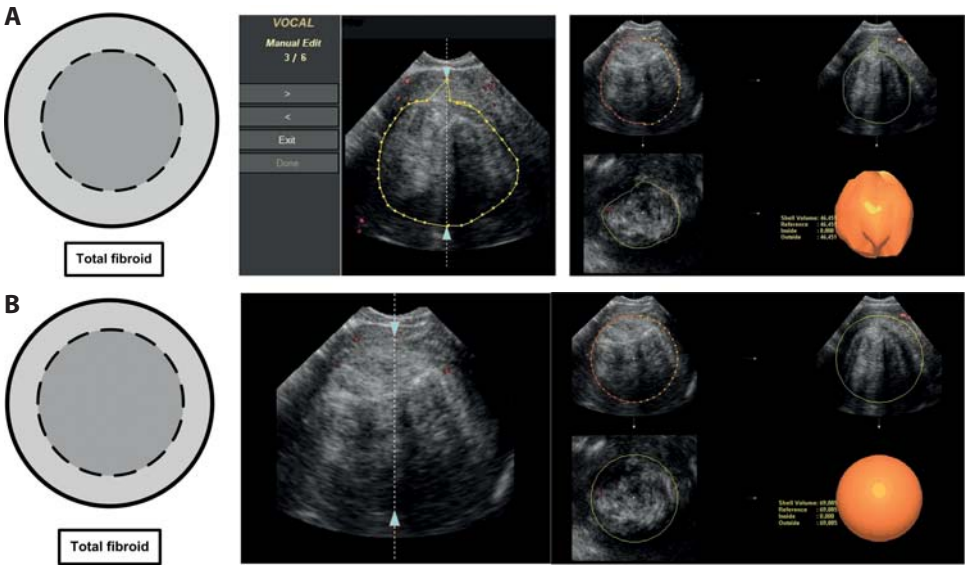


Figure 2. Method of fibroid volume calculation using 3D Power Doppler. In both the automatic sphere contour (2b) and manual contour (2a) mode rotation steps of 30 degrees were used (6 different planes). The poles were placed at the boundaries of the fibroid. For the manual contour, the circumference of the fibroid had to be drawn manually in each of the total six planes. A 3D rendering image of the fibroid and its calculated volume is seen in the lower right part of both figures.

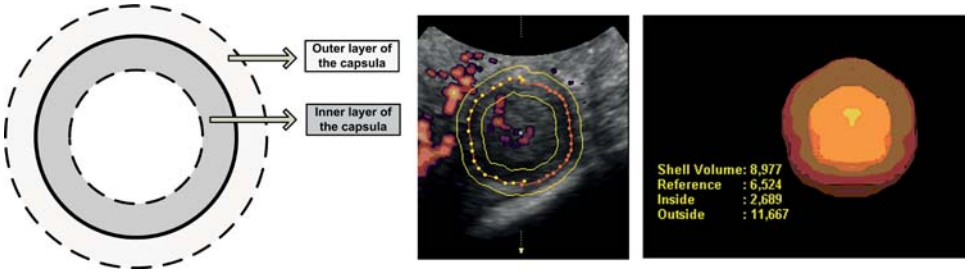


Figure 3. Method of volume measurement of the capsule of the fibroid using shell mode of 3D Power Doppler. The shell contour mode was used to measure vascularity of the capsule. The shell contour mode consists of an inner outline and an outer outline at the border of the fibroid with a total thickness of 0.5 cm. The shell contour mode can be switched on and off during volume measurement with both automatic and manual contour modes. When a volume is constructed, the shell contour mode can be switched to off, inside (inner layer on), outside (outer layer on) and symmetric (both inner and outer layer on).

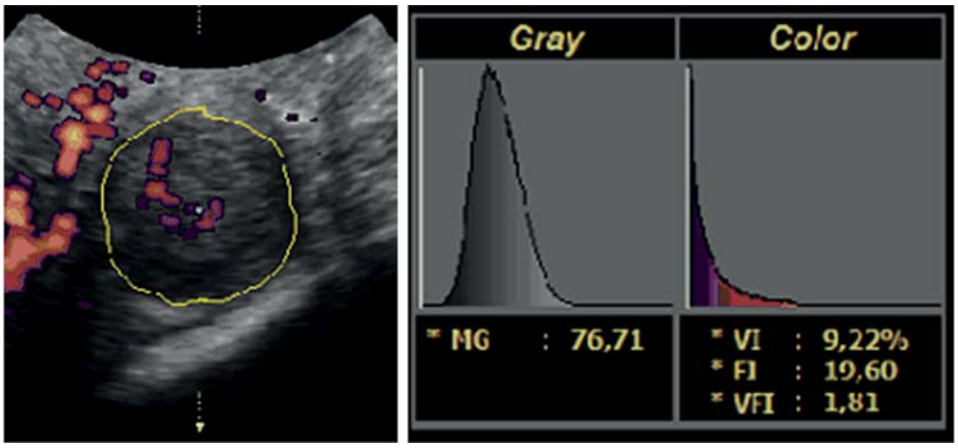


Figure 4. Measuring Vascular parameters (indices) with 3D Power Doppler. After volume acquisition, vascular indices can be obtained using the additional "histogram" function. Automatically, the vascular indices (VI, FI, VFI) are calculated of the selected volumes. VI=vascular index (% colour voxels), FI=flow index (mean intensity colour voxels), VFI= vascular flow index (average colour value of all grey and colour voxels)

Statistical analysis

IBM SPSS Statistics 20.0 software package (IBM SPSS, Washington, Illinois) was used for statistical analysis. If data were skewed, we performed a natural log transformation. Interobserver agreement of continuous variables was based on the assessment of Intraclass Correlation Coefficients (ICCs) and their related 95% CI using a two-way mixed model. An ICC value of <0.20 indicates slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement [16].

The correlation of volume and vascular parameters was calculated using Kendall's Tau test. The results from one observer were used for this analysis. The Kendall's Tau coefficient is reported in the range -1 to 1. A value of 1 represents perfect agreement and -1 perfect disagreement. When the result is zero, there is no correlation and both parameters are independent. P values < 0.05 were considered to be statistically significant. In order to identify the best discriminating vascular parameter (i.e. the parameter with the highest intraclass correlation and with the widest range between the fibroids), Box and Whisker plots of the parameters were made according to the different methods of volume acquisition with a high interobserver agreement (ICC outcome ≥0.79). To obtain an impression of the correlation between the subjectively evaluated vascularity and the

calculated vascularity of the fibroid, capsule and centre of the fibroid, we plotted the results of the subjective evaluated vascularisation and the calculated (automatic and manually acquired) VI in Box and Whisker plots.

RESULTS

Baseline characteristics

We examined nineteen women. Baseline characteristics of the patient, their fibroids and the acquired US images are listed (table 1). Patients were referred for heavy menstrual bleeding, pain, bulk symptoms or sub fertility. Mean subjective vascularity classification (on a scale of 1 to 5) of the fibroid and the capsule were 2.8 (SD 1.8) and 2.7 (SD 1.7), respectively.

Table 1. Baseline Characteristics

PATIENT CHARACTERISTICS	MEAN (STANDARD DEVIATION)
Age	42.3 (6.2)
BMI (body mass index)	23.7 (2.9)
Mean number of fibroids/patient	2.1 (1-4)
Indication for the ultrasound	Number (%)
Menorrhagia	4 (21.0)
Menorrhagia and abdominal pain	4 (21.0)
Abdominal pain	1 (5.3)
Bulk symptoms	3 (15.8)
Subfertility	4 (21.0)
Other	3 (15.8)
Fibroid characteristics	Number (%)
Fibroid shape	
Round	9 (47.4)
Elliptoid	7 (37.4)
Other	3 (15.8)
Localization of fibroid	
Subserosal	7 (37.4)
Intramural	10 (53.0)
Submucous	2 (10.5)
Texture of fibroid	
Homogenous	7 (36.7)
Intermediate	6 (31.5)
Heterogenous	6 (31.5)

Volumes and vascular parameters

In general the manually acquired contours resulted in slightly larger mean volumes compared to automatically acquired contours (table 2). Mean values of Vascular Index (VI), Flow Index (FI) and Vascular Flow Index (VFI) of different outlines of all fibroids are presented in table 2.

Table 2. Vascular outcome (VI, FI, VFI†) using 3D Power Doppler for various fibroid outlines

PARAMETERS	VOLUME CM3 MEAN (SD)	VI MEAN (SD¶)	FI MEAN (SD)	VFI MEAN (SD)
Manual contour Fibroid	70.9 (66.6)	1.8 (2.5)	24.1 (14.2)	0.7 (1.1)
Manual contour Capsula	77.0 (54.0)	2.6 (3.5)	30.8 (15.9)	1.2 (2.1)
Automatic contour Fibroid	49.8 (50.2)	1.5 (2.5)	20.0 (14.3)	0.5 (1.2)
Automatic contour Capsula	60.1 (43.5)	2.6 (3.6)	28.8 (15.2)	1.2 (2.2)
HVA§ automatic sphere	2.3 (0.4)	4.1 (5.7)	18.0 (18.6)	0.4 (3.2)

Results of one observer (HBR) are presented

†VI=vascular index (% colour voxels), FI=flow index (mean intensity colour voxels), VFI= vascular flow index (average colour value of all grey and colour voxels § high vascular area. ¶ Standard Deviation

Interobserver agreement of the vascular parameters

In general, the VI parameters showed higher ICC's than FI or VFI parameters of the acquired fibroid outlines (table 3). The manually acquired contours of the VI of the fibroid and the fibroid capsule had the best ICC; 0.89 (95% CI; 0.78-0.95) and 0.87 (95% CI; 0.70-0.94), respectively. In contrast, the ICC of the VI of the HVA was rather low ICC 0.36 (95% CI; 0.01-0.72).

Table 3. Interobserver agreement (between three observers) for three dimensional Power Doppler parameters (VI, FI, VFI†)

PARAMETERS	VOLUME (CM3) ICC (95%CI)	VI ICC (95%CI)	FI ICC (95%CI)	VFI ICC (95%CI)
Manual contour Fibroid	0.76 (0.57-0.89)	0.89 (0.78-0.95)	0.77 (0.56-0.89)	0.68 (0.42-0.87)
Manual contour Capsula	0.57 (0.10-0.83)	0.87 (0.74-0.94)	0.69 (0.47-0.85)	0.86 (0.70-0.94)
Automatic contour Fibroid	0.83 (0.67-0.92)	0.79 (0.58-0.91)	0.56 (0.28-0.80)	0.68 (0.41-0.86)
Automatic contour Capsula	0.63 (0.29-0.84)	0.79 (0.60-0.91)	0.71 (0.48-0.87)	0.70 (0.44-0.88)
High Vascular Area	0.14 (-0.05-0.43)	0.36 (0.01-0.72)	0.05 (-0.22-0.46)	0.34 (0.03-0.72)

Interobserver agreement is expressed with the Intraclass Correlation Coefficient with a 95% confidence interval.

† VI=vascular index (% colour voxels), FI=flow index (mean intensity colour voxels), VFI= vascular flow index (average colour value of all grey and colour voxels)

Correlation with volume and subjective classification

Volume and VI for both fibroid and fibroid capsule in the manual mode were not correlated, Kendall's Tau being 0.029 (95% CI -0.3163 – 0.3751) and -0.135 (95% CI -0.484 – 0.215), respectively. These values correspond with non-significant p-values (respectively 0.86; 0.42). Volume and VI for both fibroid and fibroid capsule in the automatic mode were also not correlated, Kendall's Tau 0.111 (95% CI -0.208 – 0.430) and -0.006 (95% CI -0.363 – 0.351), respectively, corresponding with non-significant p-values (respectively 0.51; 0.97). Thus VI is independent of the fibroid volume. Vascularity Index of the fibroid and VI of the capsule were related with Kendall's Tau of 0.76 (95% CI 0.58 – 0.93), p value <0.0001.

Discriminating ability of the vascular parameters

Regarding vascular parameters, the VI showed the largest range. A large range indicates the possibility of a test to give different results in different fibroids. Figure 5 shows the VI and its range for six different fibroid outlines; the manually acquired VI of the fibroid, the automatically acquired VI of the fibroid, the manually acquired VI of the capsule, the automatically acquired VI of the capsule, the centre of the fibroid and of the HVA are plotted. Figure 5 demonstrates that VI measured in manual contour mode showed the widest range (with the best interobserver agreement and independent of their volume), which indicates that the VI of various fibroid outlines measured in the manual mode have the best discriminating ability.

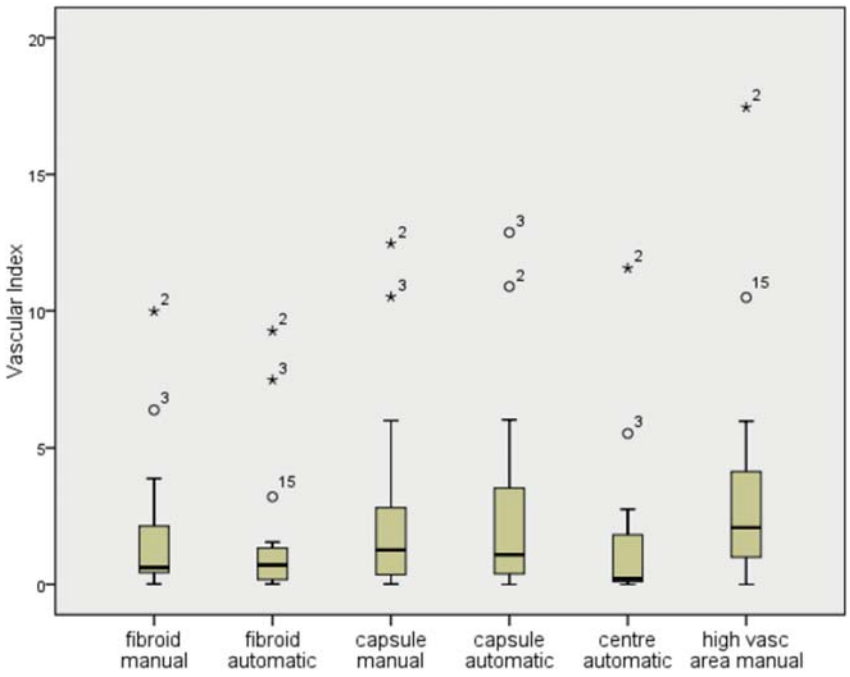


Figure 5. Range of Vascular Index* for various methods of outlining the fibroid § to estimate discriminating potential of the VI. * Vascular Index is the number of colour voxels divided by the total number of both colour and grey voxels, representing the proportion of blood vessels within the tissue. § Six types of fibroid outlines are plotted: the manually acquired VI of the fibroid, the automatically acquired VI of the fibroid, the manually acquired VI of the capsule, the automatically acquired VI of the capsule, the centre of the fibroid and of the highest vascular area (manually)

The correlation between the subjective classification of vascularity and the corresponding VI values of the fibroid, capsule and centre are plotted in Box and Whisker plots (figure 6). In general, the subjective classification of the vascularity corresponds well with the measured VI of all fibroid outlines acquired in the manual contour mode (figure 6). The best correlation was seen for the manual contour mode of the capsule (figure 6B).

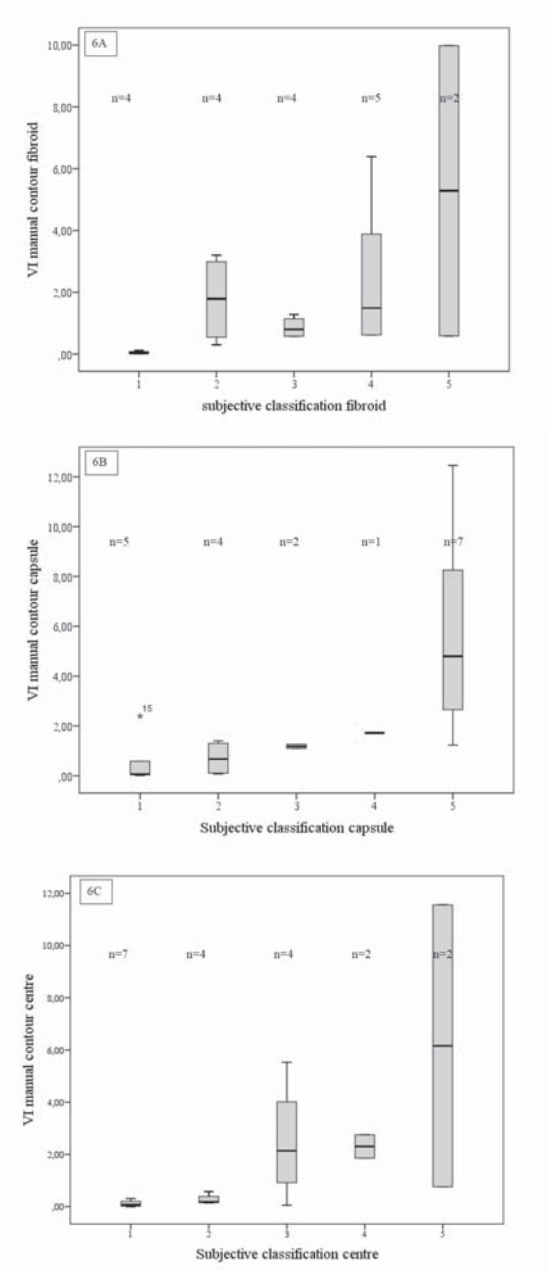


Figure 6. Correlation between Vascular Index (VI) and subjective classification of the vascularity * of different fibroid outlines measured with manual contour mode. 6A: Fibroid, 6B: Capsule of the fibroid, 6C: Centre of the fibroid. * Subjective classification of the vascularity was scored by one observer on a 1 to 5 likert scale. '1' meaning poorly vascularised and '5' highly vascularised.

DISCUSSION

To our knowledge, this is the first publication reporting reproducibility of various 3D Power Doppler parameters in the assessment of vascularity in fibroids.

Main findings

Despite the fact that we included a random sample of fibroids without excluding women with suboptimal images, we found an almost perfect interobserver agreement for various vascular parameters in stored 3D volume datasets. VI was found to be the most reproducible 3D PDUS parameter (over FI and VFI). In particular, both the manually acquired Vascular Index (VI) of the complete fibroid and the fibroid capsule showed perfect agreement. The VI parameter also showed good discriminating ability. Measured vascularity (VI) was independent of fibroid volume. Vascularity of the fibroid and the capsule were related.

In contrast to previously reported substantial interobserver agreement of the HVA in the assessment of vascularity in vascularised cystic-solid or solid adnexal masses [17;18], the subjectively selected high vascular area in our study showed a low interobserver agreement and may be considered as less useful in the assessment of the vascularity in fibroids. Several explanations can be postulated for the rather low agreement of the HVA in our study. It is likely that not all observers took the same location within the volume for the assessment of the HVA. We assume that in general the delineation of the HVA is clearer in ovarian masses than in fibroids. The distinction between solid, vascularised parts in an ovarian tumour and the anechoic fluid parts might make the sampling more reproducible than in fibroids. Penetration of the US in large fibroids was in some cases suboptimal resulting in unclear delineation of the fibroid. We hypothesise that this includes a risk of incorrect inclusion of uterine arteries in the HVA by some observers.

Strengths and weaknesses of the study

We proposed a manner for the analysis of 3D PDUS volume datasets to quantify fibroid vascularity. All examinations were made in a standardised way by an experienced examiner. We studied all possible vascular parameters of all possible relevant fibroid locations using both manual and automatic contour modes. The off-line evaluations of these parameters were performed by three independent examiners in a standardised manner, blinded for the evaluations of the other examiners or clinical information.

In retrospect, the uterine artery is sometimes difficult to distinguish from the vessels of the vascular capsule, in particular in large fibroids due to insufficient quality of the saved volumes. In future studies, more attention should be paid to the acquisition of volumes

to overcome this problem. We advise evaluating the acquired volume on completeness and image quality immediately after acquisition of the sweep (keeping in mind that not all fibroids fit into the scanning field, even with abdominal US). In the case of suboptimal image quality, a new volume should be obtained by adjusting the region of interest and/or angle of the sweep.

Clinical implications

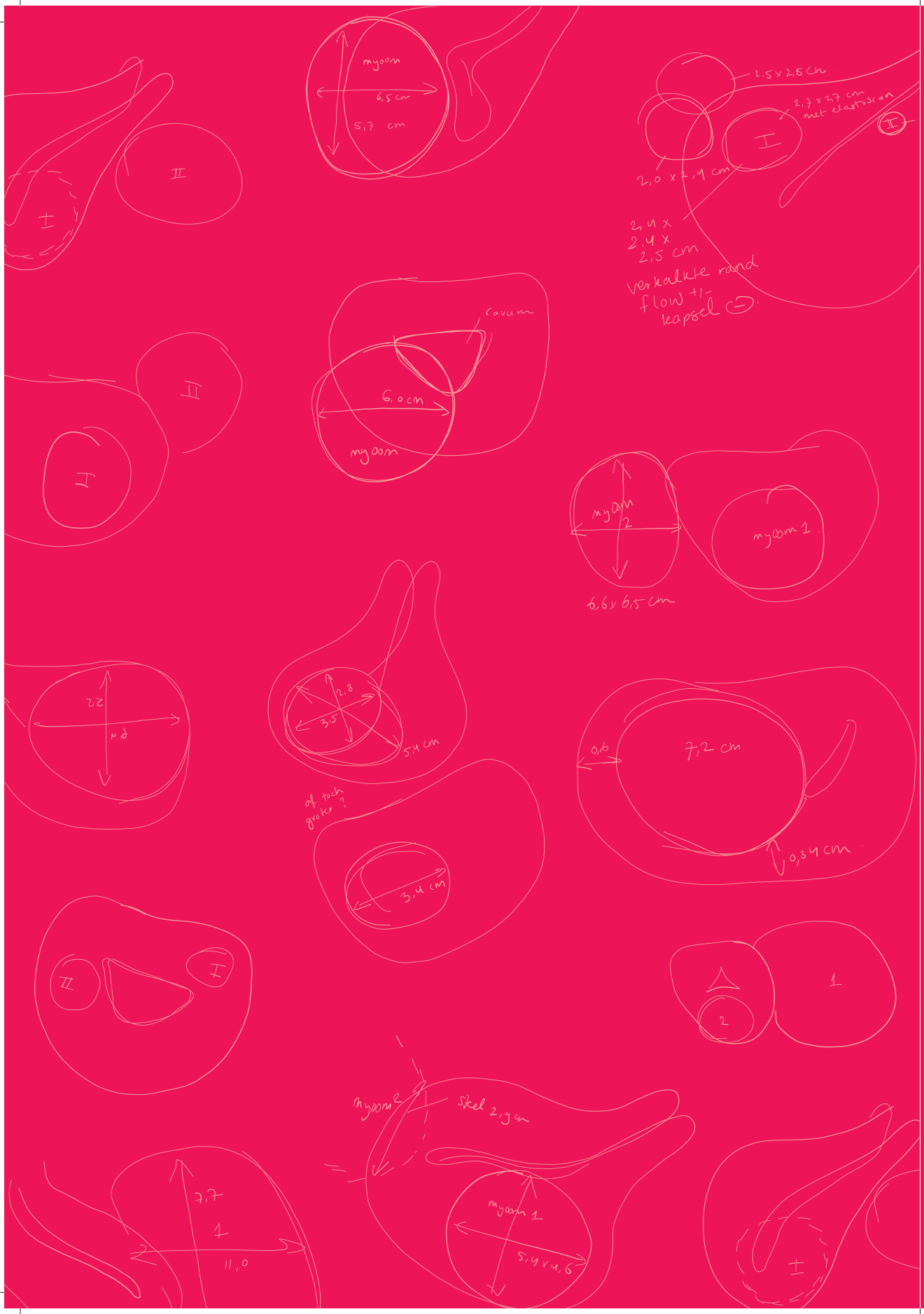
An almost perfect reproducibility of a new technique in measuring vascularity of fibroids is important to be able to further investigate the clinical relevance. In our study we did not compare results with a golden standard (vascularisation at histology). Up till now, only one observational cohort study reported a significant correlation between 3D PDUS parameters (VI and VFI) and histological parameters [11]. Vascularity as a predictor of minimally invasive treatment is mainly measured using MRI, which is expensive and time-consuming. Bearing existing knowledge in mind, we hypothesise that 3D PDUS can be used in predicting the natural course of fibroids and the response to different therapies. This suggests that there might be a role for 3D PDUS in the individual clinical management of patients with fibroids. Absolute values of VI are dependent on the US machine used, its settings and possibly also on the moment of volume acquisition during the diastolic or systolic phase [19]. Therefore our results should be interpreted with caution and we should be cautious in extrapolating our results to other situations and settings. Future studies are required to confirm our results, to validate 3D PDUS parameters with real vascularity in fibroids, and to study its clinical relevance. It might be helpful to perform a 4D recording and calculate the mean VI, in order to avoid the influence of the cardiac cycle [20].

In conclusion, VI measured by 3D PDUS is a reproducible parameter in the assessment of fibroid vascularisation with discriminating abilities.

REFERENCES

1. Wegienka G, Baird DD, Hertz-Picciotto I, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol 2003 Mar;101:431.
2. Kjerulff KH, Langenberg P, Seidman JD, et al. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med 1996;41:483.
3. Brandsborg B, Dueholm M, Kehlet H, et al. Mechanosensitivity before and after hysterectomy: a prospective study on the prediction of acute and chronic postoperative pain. Br J Anesth 2011;107:940.
4. Brolmann HA, Vonk Noordegraaf A, Bruinvels D. Can prolonged sick leave after gynaecologic surgery be predicted? An observational study in the Netherlands. Surg Endosc 2009;23:2237.
5. Volkers NA, Hehenkamp WJ, Birnie E, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome grom the randomized EMMY trial. Am J Obstet Gynecol 2007;196:1.
6. Kooij van der SM, Hehenkamp WJ, Volkers NA, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol 2010;203:105.
7. Funaki K, Fukunishi H, Sawada K. Clinical outcomes of magnetic resonance-guided focused ultrasound surgery for uterine myomas: 24-month follow-up. Ultrasound Obstet Gynecol 2009 Nov;34:584.
8. Isonishi S, Coleman RL, Hirama M. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. Am J Obstet Gynecol 2008;198:270.
9. Funaki F, Fukunishi H, Funaki T, et al. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. Am J Obstet Gynecol 2007;196(2):e1-e6.
10. Yoon SW, Lee C, Kim KA, et al. Contrast-Enhanced Dynamic MR Imaging of Uterine Fibroids as a Potential Predictor of Patient Eligibility for MR Guided Focused Ultrasound (MRgFUS) Treatment for Symptomatic Uterine Fibroids. Obstet Gynecol Int 2010.
11. Minsart AF, Ntoutoume SF, VAndenhoute K, et al Does three-dimensional power Doppler ultrasound predict histopathological findings of uterine fibroids? A preliminary study. Ultrasound Obstet Gynecol 2012 Dec;40:714.
12. Raine-Fenning NJ, Clewes JS, Kendall NR, et al. The interobserver reliability and validity of volume calculation from three-dimensional ultrasound datasets in the in vitro setting. Ultrasound Obstet Gynecol 2003 Mar;21:283.
13. Di Tomasso S, Massari S, Malvasi A, et al. Gene expression analysis reveals an angiogenic profile in uterine leiomyoma pseudocapsule. Mol Hum Reprod 2013 Jun;19:380.
14. Tinelli A, Malvasi A, Rahimi S, et al. Myoma pseudocapsule: a distinct endocrino-anatomical entity in gynecological surgery. Gynecol Endocrinol 2009 Oct;25:661.

15. Walocha JA, Litwin JA, Miodonski AJ. Vascular system of intramural leiomyomata revealed by corrosion casting and scanning electron microscopy. Hum Reprod 2003 May;18:1088.
16. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977 Mar;33:159.
17. Alcazar JL, Prka M. Evaluation of two different methods for vascular sampling by three-dimensional power Doppler angiography in solid and cystic-solid adnexal masses. Ultrasound Obstet Gynecol 2009;33:349.
18. Geomini, P.M.A.J., Coppus S, Kluivers KB, et al. Is three-dimensional ultrasonography of additional value in the assessment of adnexal masses? Gynecol Oncol 2007;106:153.
19. Kudla MJ, Alcazar JL. Spatiotemporal image correlation using high-definition flow: a new method for assessing ovarian vascularization. J Ultrasound Med 2010 Oct;29:1469.
20. Kudla MJ, Alcazar JL. Spatiotemporal image correlation with spherical sampling and high-definition flow: new 4-dimensional method for assessment of tissue vascularization changes during the cardiac cycle: reproducibility analysis. J Ultrasound Med 2012 Jan;31:73.


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

07

3D Power Doppler in uterine fibroids; influence of gain, cardiac cycle and off-line measurement techniques

L.L. Nieuwenhuis
W.J.K. Hehenkamp
H.A.M. Brölmann
J.A.F. Huirne

J Obstet Gynaecol. 2017 Aug 7:1-7. DOI:10.1080/01443615.2017.1330323

ABSTRACT

Objective: To evaluate the influence of the cardiac cycle and different gain settings on 3D PD indices in the assessment of fibroid vascularisation.

Material and methods: In 40 patients, 3D PD US was performed using 3 different gain settings: a fixed predetermined gain (50dB), a higher gain (65dB) and an individualised subjectively most optimal gain. Two consecutive 3D PD sweeps were taken to evaluate the effect of the cardiac cycle. For off-line measurements, one reviewer recorded the most favourable method of volume calculation and shell size in every fibroid.

Results: There was no statistical difference in VI between the subjective most optimal gain and the predetermined fixed gain (mean difference VI -0.31 [95%CI -0.73 to 0.12], p 0.15). No difference in VI values between two consecutive sweeps was found (mean difference VI 0.04 [95%CI -0.32 to 0.40], p 0.82). Volume calculation using the manual mode was prefered over the automatic mode in the majority of cases (65%). A shell of 0.5 cm seemed the best fit to calculate vascularisation of the fibroids' capsule.

Conclusion: To determine vascularity using 3D PD US in uterine fibroids a predetermined fixed gain can be used. By performing a scan of more than 10 seconds, the potential influence of the cardiac cycle on the VI seems limited.

Keywords: Fibroid, Leiomyoma, 3D Power Doppler, Vascularisation, Machine settings.

INTRODUCTION

Minimally invasive therapies like uterine artery embolization and MR guided focused ultrasound are emerging alternatives for hysterectomy. Vascularity of fibroids may play a role in the effectiveness of these minimal invasive techniques [1-4]. Vascularity assessment with MRI is expensive and not available for every patient. A cheaper and faster way to measure and quantify vascularisation would be preferable.

3D Power Doppler ultrasound can quantify vessels within a volume of interest and is easily performed. 3D PD ultrasound is studied extensively in several areas of gynaecology and obstetrics (uterus, ovarian, endometrium, tumour, placenta, etc). Several studies suggest that 3D PD indices may be helpful to distinguish between benign and malignant lesions [5-7].

Only a handful of investigators used 3D PD in the assessment of fibroids. Vascularity was used to assess painful myomas in pregnancy [8], response to GnRHa [9], to compare 3D PD with their histopathological parameters [3] and to assess response to Ulipristal [10]. A positive relation between 3D Power Doppler parameters and histopathological vascular parameters in fibroids is reported; high 3D PD indices correspond with high cellular activity score [3]. Furthermore, 3D PD is reported to be a reproducible technique, also in fibroids [3, 11-15].

Vascular indices are however subjective to machine settings and hardly studied in fibroids. Several factors like the cardiac cycle and machine settings have been evaluated [16-20] and have been reported to be of influence. From all machine settings, the gain has been reported to be the most sensitive to changes. A general guideline or consensus on how to use 3D PD in fibroids is lacking in terms of used settings and off-line methods to calculate vascular indices in fibroids. Therefore the aim of this study is to evaluate different gain settings and the potential influence of the cardiac cycle on 3D PD indices in the assessment of fibroid vascularisation. Secondly, several off-line methods will be evaluated for volume, shell and VI calculation in fibroids. MATERIALS AND METHODS

Study design

A prospective cohort study was performed between March 2012 and August 2014 at our out-patient clinic of the VU University Medical Centre, Amsterdam [21]. All pre-menopausal women diagnosed with a maximum of 2 fibroids without the use of any hormonal drug therapy (e.g. oral contraceptives, levonorgestrel releasing intra uterine device, GnRH agonists, Ulipristal) were consecutively asked to participate in the study and included A maximum of 2 fibroids was chosen (of which only the largest was measured) to avoid

any risk of mixing measurements of the fibroids in the same patient during follow up. During follow up, extra 3D PD sweeps were performed in a random sample of 40 patients to evaluate the effect of the cardiac cycle and gain settings. The study was approved by the ethical board as transvaginal ultrasound is considered regular care.

Ultrasound

All women underwent a real time 2D greyscale sonography of the uterus and ovaries followed by a 3D Power Doppler ultrasound on the day of their visit using a 5-8 MHz vaginal transducer on the Accuvix V10 ultrasound machine (Samsung-Medison, South Korea). All volumes were collected by a single experienced examiner (L.L. Nieuwenhuis) in a standardised way using the same predetermined settings for 3D PD. First the uterus was examined in both the sagittal (from left to right) and transversal plane (from cervix to fundus). Subsequently the myometrium was studied and in case of a fibroids, size, subjective vascularisation and location were registered. Location was classified according to the FIGO Palm Coin classification [22] . As long as the fibroid could be visualised using the vaginal probe there was no minimum or maximum fibroid diameter, however in general it was difficult or not possible to properly measure fibroids larger than 8cm. Power Doppler settings were set to achieve maximum sensitivity for detecting small vessels without background noise; Frequency 5-8 MHz, Gain fixed at 50dB, pulse repetition frequency 0.60 kHz, Wall motion filter low. The Power Doppler mode was activated and the 3D region of interest was manually adjusted to contain the entire fibroid (sweep angle of 70 to 90 degrees, dependent on the size of the fibroid).

In total 4 consecutive 3D PD sweeps were obtained: the first two sweeps with the same settings were performed to assess the effect of the cardiac cycle on the vascularisation of the fibroid. A 3D PD sweep (of 10 seconds for a small angle sweep) will include approximately 4-5 cardiac cycles (assuming a heart rate above 50 beats a minute). The last two sweeps were obtained with different gain settings. First, gain settings were changed to a higher sensitivity (a randomly chosen fixed gain 65) and then changed into what subjectively seemed the best gain. This individualised gain was selected by increasing the gain until noise artefacts were visible, followed by reducing the gain until artefacts just disappeared [16]. All acquired volumes were digitally stored (as mvl and VOO files).

Off-line evaluation of the 3D Volumes

All stored volumes were evaluated with VOCAL (Virtual Organ Computer-aided AnaLysis) software, Sonoview Pro- 1.6.2. (Samsung-Medison, South Korea). Through a standardised protocol, volume and vascular parameters were measured for the entire fibroid and for

the fibroids shell using automatic and manual modes [15]. 3D sweep quality was scored on a Likert scale from 1 to 5 for different US entities , 1 point for each entity (1. contrast, sharpness, brightness, 2. visibility of fibroid (border), 3. penetration depth, 4. total fibroid visible in sweep, 5. movement artefacts). For every volume measurement the examiner registered which type of contour (manual or automatic) subjectively seemed to be the best fit for the fibroid. The vascular parameters were automatically calculated in the histogram function of the VOCAL software. We used the VI (and not FI or VFI) since this parameter was reported to be the most reproducible one in fibroids assessment [3, 15]. The VI represents the proportion of blood vessels within the tissue (number of colour voxels divided by the total number of both colour and grey voxels). To assess the optimal shell thickness for fibroids, two different shells sizes were compared; shell thickness of 0.5 cm and 1 cm. The optimal shell contour should contain the entire vascular capsule without other uterine vessels such as (branches of) the uterine arteries.

Statistical analysis

All analyses were performed using IBM SPSS Statistics 22.0 software package.

A paired t-test was used to compare the effect of different gain settings on the vascularisation index (VI) and to compare the difference in VI from two consecutive sweeps (p value <0.05 was considered statistically significant). If data were not normally distributed, they were log transformed. RESULTS

Baseline characteristics of patients and fibroids are listed in Table 1. The vast majority of 3D sweeps was of sufficient or good quality (94.3 %). Only in 1.4% of 3D sweeps quality was insufficient for proper VI assessment and were excluded, in all of these volumes it concerned a large fibroid.

Gain settings

Data were not normally distributed and therefore log transformed before analyses. The average subjective most optimal gain (chosen by the examiner) was 48.13dB (SD 7.6, median 48, range 38-60). The VI of the predetermined fixed gain (gain 50dB) and the chosen subjective most optimal gain did not differ significantly with a mean difference in VI value of -0.30 (95%CI -0.73 to 0.12; p value 0.15) (Table 2). The VI of the higher gain setting (gain 65) was significantly higher than the standard gain of 50 with a mean difference of 0.62 (95% CI 0.29 to 0.94; p value <0.01).

Table 1. Baseline patient and fibroid characteristics

PATIENT AND FIBROID CHARACTERISTICS	N=40
Age	
Mean (SD)	41.53 (7.06)
Range	30-52 year
Parity	
0	28.6%
≥ 1	71.4%
Ethnicity	
North European	39.4%
Other	60.6%
Symptoms	
Heavy menstrual bleeding	32.2 %
Pain/Bulk symptoms	35.7 %
Combination of symptoms	10.7 %
Non fibroid related symptoms	21.4 %
Number of fibroids	
1	64.3 %
>1	35.7 %
Fibroid size (diameter in cm)	
Mean (SD)	4.33 cm (1.93)
Range	1.5-8.8 cm
Fibroid location	
Submucosal (FIGO* 0-2)	3.6 %
Intramural (FIGO 3-5)	60.7 %
Subserosal (FIGO 6-7)	35.7 %

*Fibroid classification according to the FIGO (PALM-COIN) classification

Table 2. Effect of the cardiac cycle and different gain settings on Vascular Index (VI) measured with 3D Power Doppler ultrasound in patients with fibroids (N=40)

	MEAN VI	MEAN DIFFERENCE	95% CI	P-VALUE*
Sweep 1 vs sweep 2 #	0.97 / 0.93	0.04	-0.32 to 0.40	0.82
Gain 50 dB vs chosen gain §	0.88 / 1.19	-0.31	-0.73 to 0.12	0.15
Gain 50 dB vs gain 65 dB	0.98 / 1.82	0.84	0.29 to 0.94	<0.01

* p-value of <0.05 was considered statistically significant, fibroid volumes were not normally distributed therefore values were log transformed

Two consecutive 3D PD sweeps were performed and considered representative to investigate influence of the cardiac cycle. Patients had at least 4 cardiac cycles during 3D PD sweep recording

§ The chosen gain was an individualised gain obtained by increasing the gain until noise artefacts were visible followed by reducing the gain until artefacts just disappeared

Potential effect of variations during the cardiac cycle

No significant difference in VI values between two consecutive sweeps was found (mean difference 0.04; 95%CI -0.32 to 0.40; p=0.82, Table 2), indicating that potential variation during the cardiac cycle does not disturb the outcome of the VI of fibroids when duration of the scan is 10 seconds or longer. However in a few individuals large differences were observed in the two consecutive measurements, all with a very high VI value (see Figure 1). It is not clear if these differences are affected by variation or are induced by the cardiac cycle.

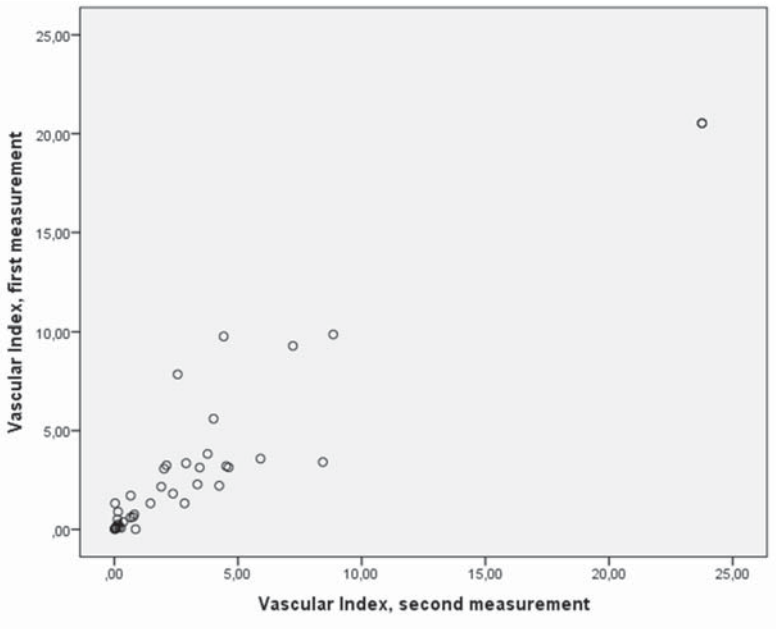


Figure 1. Vascular Index (VI)* in fibroids calculated from two consecutive 3D Power Doppler sweeps in the same patient #. *VI was measured using VOCAL software (manual contour mode, histogram function). #Little difference can be observed between two consecutive measurements. Only in a few individuals, all with a high VI, large differences can be observed.

Off-line subjective evaluations

Of the 40 patients, 4 patients had fibroids larger than 8cm (the largest diameter was 8.8 cm). Fibroids larger than 8cm did not seem to fit well in the scan sector and deeper / peripheral vessels were not visible (Figure 2) without increasing the gain resulting in noise artefacts. As far as we are aware of, there is no international agreement on optimal fibroid diameter groups to be used. For small fibroids (0-3cm), the manual and

automatic modes are both good to use. In case of a large fibroid (>6cm) or oval fibroid (Figure 3), examiner preferred to use the manual contour mode (see Table 3). The most optimal shell size seemed 0.5cm (see Table 4).

Table 3. Observer preference* for type of volume measurement in fibroids using 3D Power Doppler ultrasound and VOCAL software

	MANUAL [#]	AUTOMATIC[§]	NO PREFERENCE
Fibroids 0-3cm	5	0	6
Fibroids 3-6cm	15	0	8
Fibroids >6cm	6	0	0
Total fibroids N=40	26	0	14

* Observer preference was noted based on several items expecting volume contour to exactly match fibroid's contour.

[#] For the manual contour mode, the poles were placed at the boundaries of the fibroid and the circumference of the fibroid had to be drawn manually in six planes (rotation steps of 30 degrees)

[§] For the automatic contour mode, the poles were placed at the boundaries of the fibroid and a sphere contour was chosen which automatically generated a volume

Table 4. Shell size preference* in measuring vascular indices using 3D Power Doppler ultrasound and VOCAL software for the capsule of the fibroid [#]

	SHELL 0.5CM	SHELL 1CM	NO PREFERENCE
Fibroids 0-3cm	11	0	0
Fibroids 3-6cm	19	1	3
Fibroids >6cm	3	1	2
Total fibroids N=40	33	2	5

*Observer preference was noted based on several items expecting the optimal shell contour to contain the vascular capsule only (and should not contain vessels outside the capsule or miss part of the vascular capsule).

[#] After fibroid volume measurement a symmetrical shell contour was chosen of 0.5 or 1cm.

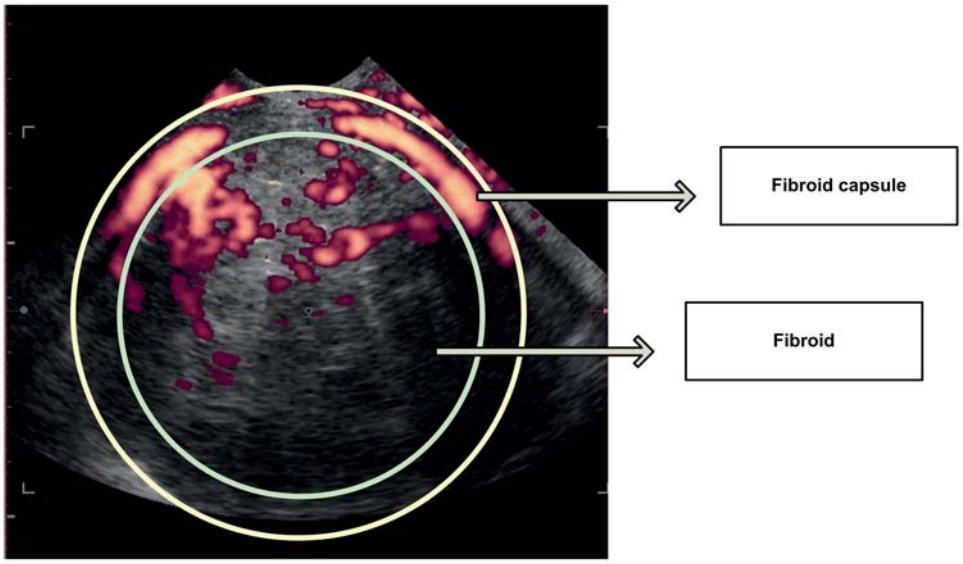


Figure 2. 3D Power Doppler image: well vascularised fibroid, moderate peripheral penetration

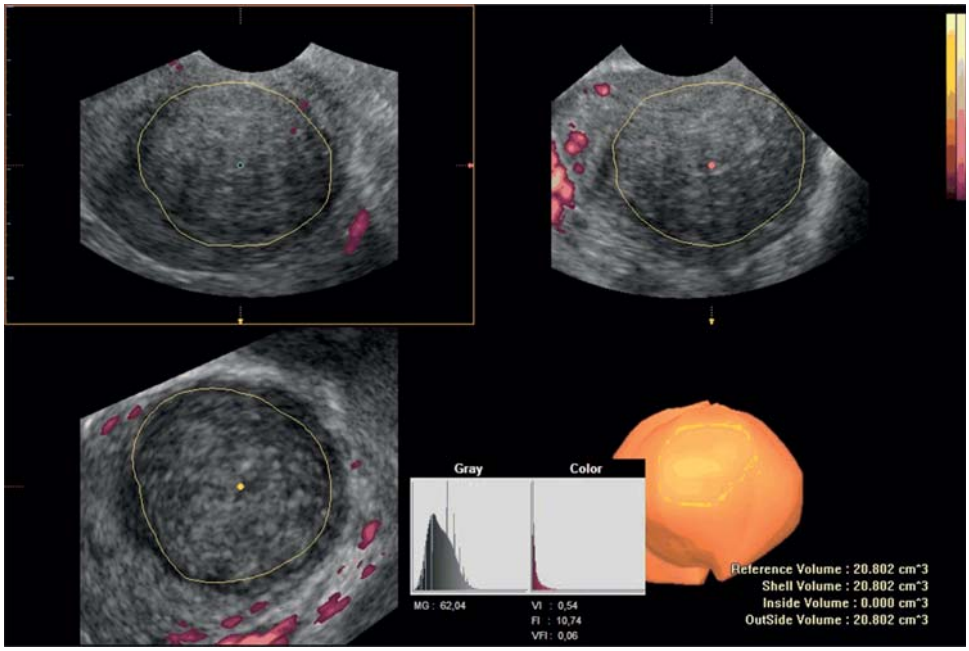


Figure 3. 3D Power Doppler image in VOCAL: oval fibroid with vascular capsule, good peripheral penetration

DISCUSSION

Main findings

A predetermined most optimal fixed gain setting was not different from a individually most optimal chosen gain in vascular assessment of fibroids using 3D PD. A higher gain corresponded with a significantly higher VI. Furthermore, the cardiac cycle does not exert a major impact on fibroid vascularisation when duration of the scan is long (in our study it was in general 10 seconds or longer). In some individuals with a highly vascularised fibroid, its influence cannot be excluded given the variation between two consecutive volumes. For off-line fibroid volume evaluation the manual mode was preferred, especially for large fibroids. Fibroids larger than 8 cm did not seem to fit in the scan sector and may be less suited for transvaginal (3D PD) measurement. A shell of 0.5 cm seemed the best fit to calculate vascularisation of the fibroids' capsule.

Limitations

A limitation of the present study is that the assumption was made that 2 consecutive sweeps were representative enough to investigate influence of the cardiac cycle. This methodology can be debated since we did not compare VI in systole with VI in diastole. On the other hand we observed sweep time for several 3D PD sweeps, a 3D sweep of a fibroid <3cm will take 10 seconds on the used ultrasound machine and automatically contains several cardiac cycles in one volume. During the study we did not measure sweep time per 3D PD sweep taken, therefore we cannot analyse the effect of the duration of the individual sweeps taken. Machines with a faster sweep time may have a higher risk on differences due to the cardiac cycle but on the other hand may have a lower risk on movements artefacts. Given the lack of previous data we were not able to make a proper power calculation and we chose a sample size that we though was sufficient. However we are not sure if our sample size was large enough to detect differences in VI induced by variations during the cardiac cycle.

Interpretation

3D PD vascular indices are subjected to machine settings. Several effects like the cardiac cycle and machine settings are evaluated [16, 17, 19, 23-26] and reported to be of influence. Findings in our population on gain settings correspond with most studies [3, 16, 19]. A higher gain corresponds with a higher VI [16] and a predetermined most optimal gain can be used with good reproducibility and is reported to correspond with the histology [3]. Measuring fibroids over time suggest a fixed gain seems to be sufficient suitable in order to assess fibroid vascularisation but this was not studied. Yet, some studies have used the fixed gain setting already to follow patients' vascular indices [9, 10].

Several studies in fibroids did not correct for the possible influence of the cardiac cycle [3, 9, 10]. While others advice to use STIC/ 4D PD to overcome the influence of the cardiac cycle [24, 27]. For example, a significant difference was found between a 1cm3 part of ovarian stroma measured in systole and diastole [27]. In our study we measured the entire fibroid (larger than 1cm3) and could not confirm a significant influence of the cardiac cycle. A 3D sweep of a fibroid will take more than 10 seconds and automatically contains several cardiac cycles in one volume. A potential influence of the cardiac cycle is hereby possibly overcome. On the other hand, if we study the individual two measurements we can observe that in 4 patients with highly vascularised fibroids there was a large difference between both measurements. Thus a potential effect of the cardiac cycle in these conditions cannot be excluded. However differences can also be exerted due to variations in off-line volume selection for VI calculation between two sweeps, since these will never be exactly the same and can be difficult in case of large fibroids or poor image quality. Fibroids larger than 8 centimetres did not fit well in the scan sector and showed to take up fewer vessels in peripheral fibroids tissue (large distance from the transducer). This is in concordance with previous studies [10, 17, 28]. Besides ultrasound settings, off-line measurements can influence the vascular parameters as well. If fibroid volume is not measured correctly or completely this will influence the calculated volume and will subsequently influence the vascular parameters. In the present study we only evaluated the preference of one examiner concerning the best fitting off-line mode for fibroid measurement. In a previous study [15] the interobserver agreement was highest for the manual mode. In the present study we also found that in the majority of cases, the volume measurement in our hands is most reliable with the manual mode, mainly due to the size and shape (not always round but slightly oval) of the fibroid. These results need to be confirmed in future studies. We did not verify our volume measurements with other imaging modalities. However some previous studies reported fibroid volumes by 3D ultrasound to be similar to measurements by MRI or histopathology [29].

Clinical implications

Total ultrasound examination time was not recorded. In general it takes approximately 1 minute extra to make a 3D PD sweep. Off- line calculation of the VI takes approximately 2 to 5 minutes, dependent on the number of calculations made and dependent on the experience of the examiner. Possible effects on the performance of 3D PD were studied before applying it in clinical practice. Although it is not possible to overcome differences between machine settings we consider 3D PD to be useful in fibroids. A predetermined (most optimal) fixed gain setting seems to be the most accurate way to evaluate fibroid vascularisation between patients and to study vascularisation in fibroids over time. A tool to quantify vascularisation in fibroids may in theory be clinically relevant to predict

the natural behaviour of fibroids and response to drug or minimal invasive therapies. Together with the previously reported good reproducibility and correlation with histology, 3D PD can make a trustworthy instrument to apply for fibroid evaluation in clinical practise. Before applying 3D PD as a diagnostic tool in fibroids, these results need to be confirmed in other studies. The potential diagnostic effect of 3D PD ultrasound can then be further studied in clinical practise.

IN CONCLUSION

To determine vascularity using 3D PD ultrasound in uterine fibroids a predetermined most optimal fixed gain can be used. The cardiac cycle showed not to be of influence (when scan duration is more than 10 seconds), though needs to be confirmed in other studies. For off-line 3D PD volume measurement in fibroids examiner preferred the manual contour mode and a shell size of 0.5cm.

REFERENCES

1. Funaki F, Fukunishi H, Funaki T, Sawada K, Kaji Y, Maruo T. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. AJOG. 2007 2007;196(2):e1-e6.
2. Isonishi S, Coleman RL, Hirama M. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. AJOG. 2008 2008;198(3):270-e1.
3. Minsart AF, Ntoutoume SF, VAndenhoute K, Jani J, Van PC. Does three-dimensional power Doppler ultrasound predict histopathological findings of uterine fibroids? A preliminary study. Ultrasound Obstet Gynecol. 2012 12/2012;40(6):714-20.
4. Yoon SW, Lee C, Kim KA, Kim SH. Contrast-Enhanced Dynamic MR Imaging of Uterine Fibroids as a Potential Predictor of Patient Eligibility for MR Guided Focused Ultrasound (MRgFUS) Treatment for Symptomatic Uterine Fibroids. Obstet Gynecol Int. 2010 2010;2010.
5. Alcazar JL, Merce LT, Garcia MM. Three-dimensional power Doppler vascular sampling: a new method for predicting ovarian cancer in vascularized complex adnexal masses. J Ultrasound Med. 2005 5/2005;24(5):689-96.
6. Alcazar JL, Guerriero S. Three-dimensional power Doppler in ovarian tumors. Ultrasound Obstet Gynecol. 2007 6/2007;29(6):718-9.
7. Makled AK, Elmekkawi SF, El-Refaie TA, El-Sherbiny MA. Three-dimensional power Doppler and endometrial volume as predictors of malignancy in patients with postmenopausal bleeding. J Obstet Gynaecol Res. 2013 5/2013;39(5):1045-51.
8. Degani S, Tamir A, Leibovitz Z, Shapiro I, Gonen R, Ohel G. Three-dimensional power Doppler in the evaluation of painful leiomyomas and focal uterine thickening in pregnancy. Int J Gynaecol Obstet. 2007 11/2007;99(2):122-6.
9. Chia CC, Huang SC, Chen SS, Kang JY, Lin JC, Lin YS, et al. Ultrasonographic evaluation of the change in uterine fibroids induced by treatment with a GnRH analog. Taiwan J Obstet Gynecol. 2006 6/2006;45(2):124-8.
10. Czuczwar P, Wozniak S, Szkodziak P, Milart P, Wozniakowska E, Wrona W, et al. Influence of ulipristal acetate therapy compared with uterine artery embolization on fibroid volume and vascularity indices assessed by three-dimensional ultrasound: prospective observational study. Ultrasound Obstet Gynecol. 2015 6/2015;45(6):744-50.
11. Alcazar JL, Merce LT, Manero MG, Bau S, Lopez-Garcia G. Endometrial volume and vascularity measurements by transvaginal 3-dimensional ultrasonography and power Doppler angiography in stimulated and tumoral endometria: an interobserver reproducibility study. J Ultrasound Med. 2005 8/2005;24(8):1091-8.
12. Alcazar JL, Prka M. Evaluation of two different methods for vascular sampling by three-dimensional power Doppler angiography in solid and cystic-solid adnexal masses. Ultrasound Obstet Gynecol. 2009 2009;33:349-54.

13. Claeskens J, Tomsin K, Molenberghs G, Van HC, Mesens T, Meylaerts L, et al. Validation of 3D power Doppler and VOCAL software in the sonographic assessment of hepatic venous flow. Facts Views Vis Obgyn. 2013 2013;5(1):7-12.

14. Jones NW, Raine-Fenning NJ, Mousa HA, Bradley E, Bugg GJ. Evaluating the intra- and interobserver reliability of three-dimensional ultrasound and power Doppler angiography (3D-PDA) for assessment of placental volume and vascularity in the second trimester of pregnancy. Ultrasound Med Biol. 2011 3/2011;37(3):376-85.

15. Nieuwenhuis LL, Betjes HE, Hehenkamp WJ, Heymans MW, Brolmann HA, Huirne JA. The use of 3D power Doppler ultrasound in the quantification of blood vessels in uterine fibroids: feasibility and reproducibility. J Clin Ultrasound. 2015 3/2015;43(3):171-8.

16. Collins SL, Stevenson GN, Noble JA, Impey L, Welsh AW. Influence of power Doppler gain setting on Virtual Organ Computer AnaLysis (VOCAL) indices *in vivo*: Can use of the individual sub-noisegain (SNG) level optimise information? Ultrasound Obstet Gynecol. 2012 2/16/2012;epub ahead of print.

17. Martins WP, Raine-Fenning NJ, Ferriani RA, Nastri CO. Quantitative three-dimensional power Doppler angiography: a flow-free phantom experiment to evaluate the relationship between color gain, depth and signal artifact. Ultrasound Obstet Gynecol. 2010 3/2010;35(3):361-8.

18. Miyague AH, Raine-Fenning NJ, Polanski L, Martinez LH, Araujo JE, Pavan TZ, et al. Assessing repeatability of 3D Doppler indices obtained by static 3D and STIC power Doppler: a combined in-vivo/in-vitro flow phantom study. Ultrasound Obstet Gynecol. 2013 11/2013;42(5):571-6.

19. Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS, Perkins A, et al. Evaluation of the effect of machine settings on quantitative three-dimensional power Doppler angiography: an in-vitro flow phantom experiment. Ultrasound Obstet Gynecol. 2008 9/2008;32(4):551-9.

20. Schulten-Wijman MJ, Struijk PC, Brezinka C, De JN, Steegers EA. Evaluation of volume vascularization index and flow index: a phantom study. Ultrasound Obstet Gynecol. 2008 9/2008;32(4):560-4.

21. Nieuwenhuis LL, Keizer AL, Stoelinga B, Twisk JW, Hehenkamp WJ, Brolmann HA, et al. Fibroid vascularisation assessed with three dimensional Power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective cohort study. BJOG. 2017 Feb 17.

22. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011 Apr;113(1):3-13.

23. Kudla MJ, Alcazar JL. Spatiotemporal image correlation with spherical sampling and high-definition flow: new 4-dimensional method for assessment of tissue vascularization changes during the cardiac cycle: reproducibility analysis. J Ultrasound Med. 2012 1/2012;31(1):73-80.

24. Miyague AH, Raine-Fenning NJ, Pavan TZ, Polanski LT, Baumgarten MN, Nastri CO, et al. Influence of gain adjustment on 3-dimensional power Doppler indices and on spatiotemporal image correlation volumetric pulsatility indices using a flow phantom. J Ultrasound Med. 2013 10/2013;32(10):1831-6.

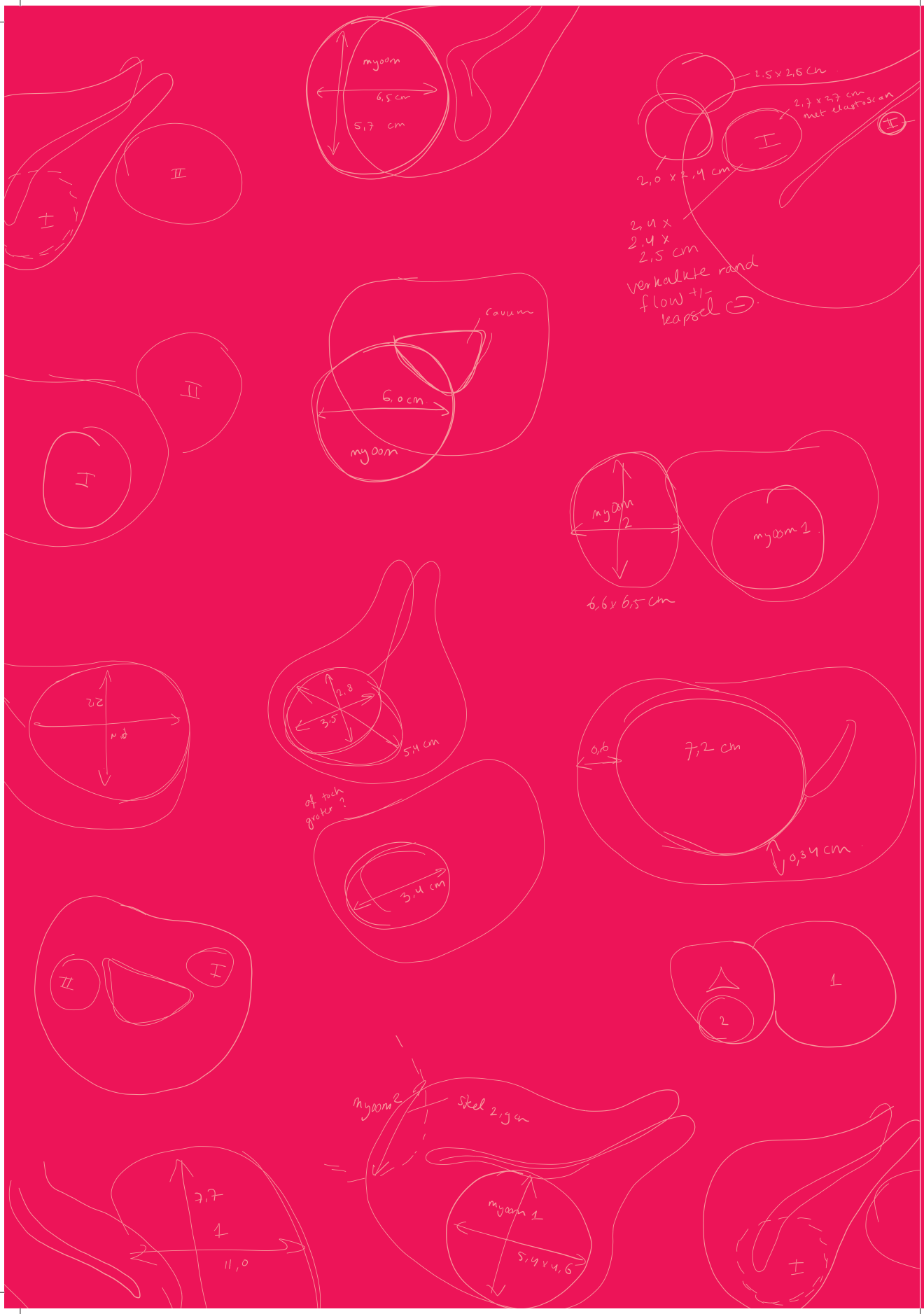
25. Ten Cate DF, Luime JJ, van der Ven M, Hazes JM, Kooiman K, de Jong N, et al. Very different performance of the power Doppler modalities of several ultrasound machines ascertained by a microvessel flow phantom. Arthritis Res Ther. 2013 Oct 24;15(5):R162.

26. Yoon DY, Choi BI, Kim TK, Han JK, Yeon KM. Influence of instrument settings on flow signal and background noise in power Doppler US. An experimental study using a flow phantom with hyperechoic background. Invest Radiol. 1999 12/1999;34(12):781-4.

27. Kudla MJ, Alcazar JL. Spatiotemporal image correlation using high-definition flow: a new method for assessing ovarian vascularization. J Ultrasound Med. 2010 10/2010;29(10):1469-74.

28. Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS, Perkins A, et al. Determining the relationship between three-dimensional power Doppler data and true blood flow characteristics: an in-vitro flow phantom experiment. Ultrasound Obstet Gynecol. 2008 9/2008;32(4):540-50.

29. Zivkovic N, Zivkovic K, Despot A, Paic J, Zelic A. Measuring the volume of uterine fibroids using 2- and 3-dimensional ultrasound and comparison with histopathology. Acta Clin Croat. 2012 Dec;51(4):579-89.


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

08

Fibroid vascularisation assessed with three dimensional Power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective cohort study

LL Nieuwenhuis
AL Keizer
B Stoelinga
JWR Twisk
WJK Hehenkamp
HAM Brolmann
JAF Huirne

BJOG. 2017 Feb 17. doi: 10.1111/1471-0528.14608

ABSTRACT

Objective. To analyse fibroid vascularisation measured with three-dimensional (3D) power Doppler in relation to absolute fibroid volume change during 12 months of follow up and in relation to fibroid growth rate per year.

Design. A prospective cohort study was performed between March 2012 and March 2014.

Setting. Outpatient clinic of the VU medical centre, Amsterdam.

Population or sample. All premenopausal women diagnosed with a maximum of two fibroids with expectant management were consecutively included.

Methods. Three-dimensional ultrasound including power Doppler was performed at baseline, 3, 6 and 12 months. Volume and vascular parameters were calculated using VOCAL software.

Main outcome measures. The relationship between vascular index (VI) at baseline and fibroid volume over time was analysed using linear mixed model analyses for repeated measurements. Second, the relationship between VI at baseline and fibroid growth rate per year was calculated using linear regression analyses. Analyses were adjusted for possible confounders.

Results. In all, 66 women (mean age 42 years) completed 12 months of follow up without treatment. Baseline fibroid vascularisation (VI) measured with 3D power Doppler is correlated with fibroid volume at 12 months ($P = 0.02$). An increase of 1% in VI at baseline was associated with a 7.00-cm^3 larger fibroid volume at 12 months. Furthermore, vascularisation was also associated with fibroid growth rate per year ($P = 0.04$).

Conclusion. In women with uterine fibroids without therapy, baseline vascularisation (VI) measured with 3D power Doppler is correlated with absolute fibroid volume change at 12 months and with fibroid growth rate per year.

Keywords. Doppler, fibroid/leiomyoma, growth, three dimensional, ultrasonography.

Tweetable abstract. Fibroid vascularisation correlates with absolute fibroid volume change and fibroid growth rate per year.

INTRODUCTION

Uterine fibroids are a common problem in women and cause a major public health-care burden.[1–3] Various known and unknown factors may affect fibroid growth.[4] Effective treatment strategies and factors predicting fibroid growth or regression are limited. There is a large variation in changes in fibroid growth; fibroids in one woman may grow at different rates and up to one-fifth of fibroids regress spontaneously in pre-menopausal women [5-8]. Determining growth potential of a distinct fibroid would profit clinical decision making. Potential fibroid growth is particularly relevant in women with limited symptoms and for women considering a (future) pregnancy. Currently there are no strong predictors for fibroid growth that can be used in daily practice.

Angiogenic growth factors play an important role in mechanisms of fibroid pathophysiology, including abnormal vasculature and fibroid growth.[9] The pathophysiology is complex and several hypotheses are made including hypoxia to stimulate angiogenesis and the formation of a fibroid capsule facilitating fibroid growth. Most fibroids have a typical vascular (pseudo)capsule that is an anatomically distinct structure surrounding the fibroid and has its own gene expression profile[10] and rich vascular network.[11,12] Fibroid vasculature and the pseudo capsule can be visualised using colour Doppler or power Doppler ultrasound. Three-dimensional (3D) power Doppler (PD) imaging is frequently used to assess the vascularity of a volume/organ. 3D PD is reported as a reproducible technique in the assessment of fibroids[13,14] and it has been used to measure vascularisation after gonadotrophin-releasing hormone analogues and ulipristal acetate therapy.[15,16] It has not yet been studied in relation to fibroid growth. Our hypothesis is that highly vascularised fibroids grow faster than poorly vascularised fibroids and that we are able to use 3D PD to predict fibroid growth rate. The aim of this study is to analyse absolute fibroid growth and fibroid growth rate during 1-year treatment-free follow up in relation to fibroid vascularisation at baseline using 3D PD ultrasound.

METHODS

Study design

A prospective cohort study was performed between March 2012 and March 2014 at our outpatient clinic, Department of Gynaecology and Obstetrics, VU University Medical Centre (tertiary referral centre for fibroids), Amsterdam. All premenopausal women diagnosed with a maximum of two fibroids without the use of any (local) hormonal drug therapy were consecutively asked to par-ticipate in the study and included.

Patients were followed at baseline, 3, 6 and 12 months. Exclusion criteria were fibroids >8 cm (there was no minimum size), more than two fibroids, adenomyosis, pregnancy and (local or systemic) hormonal or surgical therapy. A maximum of two fibroids was chosen (of which the largest was measured) to avoid any risk of mixing measurements of fibroids in the same patient during follow up. The study was listed in the Dutch Trial Register; number NTR3349 and approved by the ethics board of the VU University Medical Centre.

Ultrasound and machine settings

Two- and three- dimensional sonography including PD (Figure 1) were performed at baseline, 3, 6 and 12 months using the Accuvix V10 ultrasound machine (Samsung-Medison, Seoul, South Korea). All volumes were recorded by an experienced examiner (LLN) in a standardised way using a 3D vaginal probe (5–8 MHz) as previously published.[13,14,17,18] Settings of PD were chosen to achieve maximum sensitivity for detecting small vessels without background noise or Doppler artefacts; frequency 5–8 MHz, Gain fixed at 50 dB, pulse repetition frequency 0.60 kHz, Wall motion filter low. Size, location and subjective impression of vascularisation of the fibroid were noted and drawn schematically to ensure correct follow up.

Off-line evaluation of the 3D volumes

All stored volumes were evaluated with VOCAL software, Sonoview Pro-1.6.2 (Samsung-Medison). 3D sweep quality was scored on a Likert scale of 1–5 for different ultrasound entities, 1 point for each entity (1. contrast, sharpness, brightness, 2. visibility of fibroid (border), 3. penetration depth, 4. total fibroid visible in sweep, 5. movement artefacts). Volume and Vascular Index (VI) were calculated using the manual contour mode in VOCAL (Virtual Organ Computer-aided AnaLysis). Fibroid contours were drawn in six consecutive planes using a 30° rotation step. Power Doppler indices were then automatically calculated using the histogram function. Fibroid contours measured did not contain the capsule. The fibroid capsule was measured separately.[14] The VI represents the proportion of blood vessels within the tissue (number of colour voxels divided by the total number of both colour and grey voxels).

Statistical analysis

All analyses were performed using SPSS Statistics 22.0 soft-ware package (IBM, New York, NY, USA).

To analyse the relationship between vascularisation at baseline and absolute fibroid volume change over 12 months of follow-up linear mixed model analyses for repeated measurements were used. Mixed model analysis was used to take into account the correlation between the repeated measures within the women. Besides the relationship on average over time, also the relationship with fibroid volume at the different time points was assessed. For the latter, time was added to the analyses as a categorical variable represented by dummy variables. In addition, the same analyses were performed for the capsule of the fibroid. All analyses were adjusted for fibroid volume at baseline and second for age, parity, race, fibroid location and number of fibroids.

Additionally, the relationship between VI at baseline and fibroid growth rate per year was analysed with linear regression analysis. Fibroid growth rate per year was calculated as the difference between fibroid volume at 12 months and fibroid volume at baseline expressed as a percentage of baseline fibroid volume. Besides a crude analysis, analyses were also adjusted for age, race, parity, fibroid location and number of fibroids. A $P < 0.05$ was considered statistically significant.

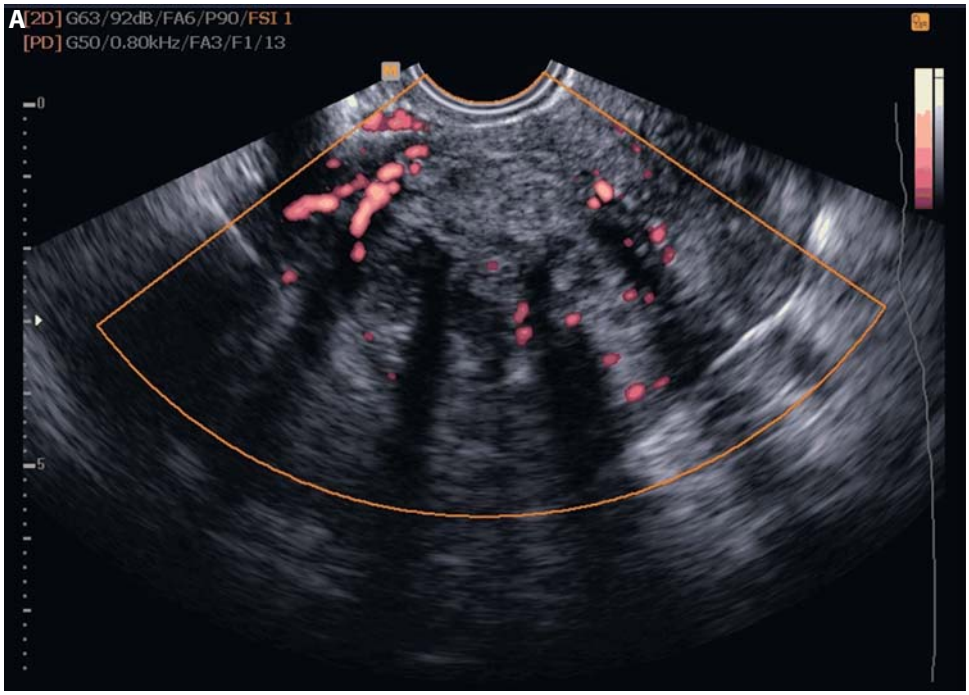


Figure 1: Three dimensional Power Doppler ultrasound (3D PD US) of a fibroid
a. Ultrasound image of a fibroid and its vascularisation visible with 3D PD SU (top)

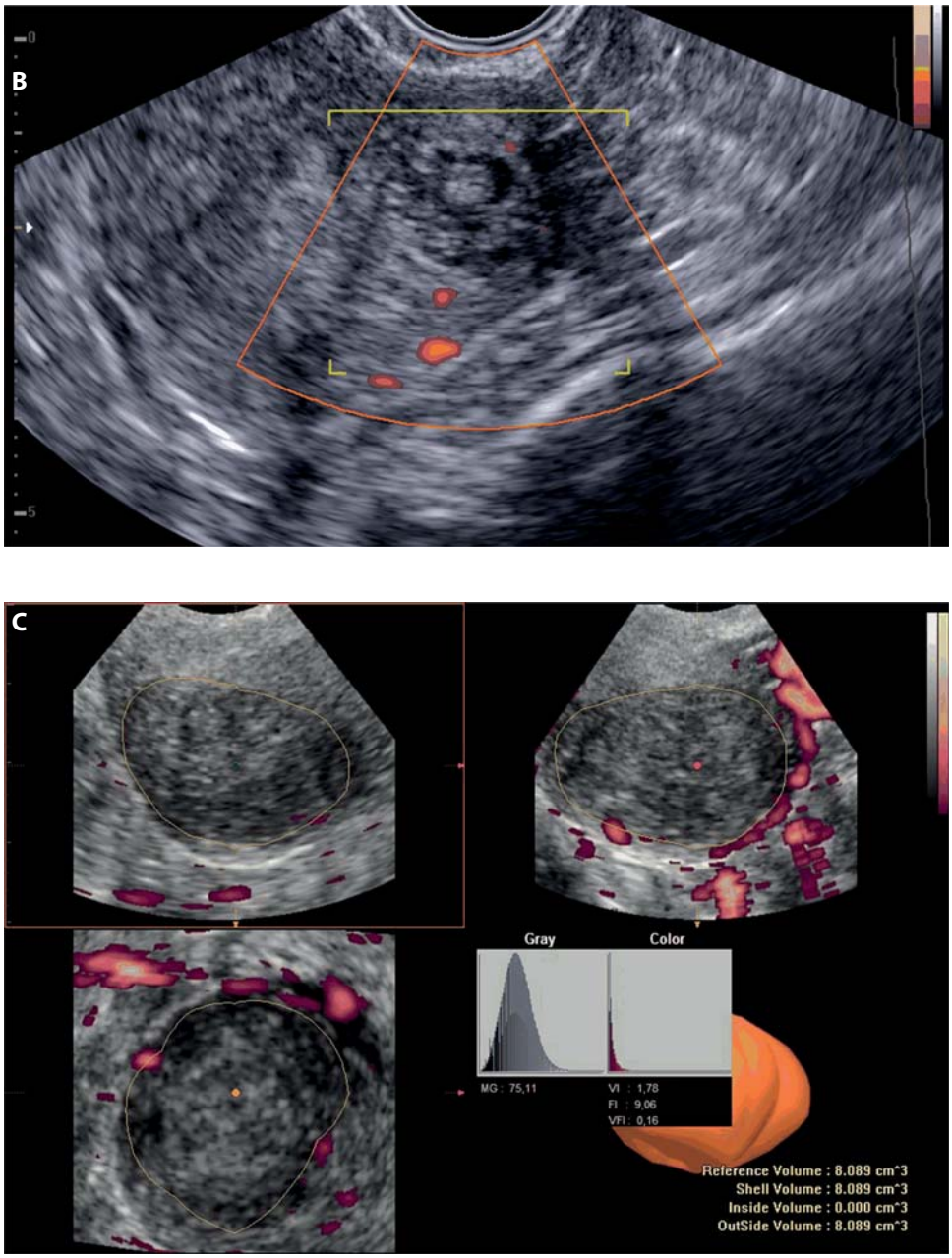


Figure 1: Three dimensional Power Doppler ultrasound (3D PD US) of a fibroid
b. A fibroid being scanned with 3D PD US (middle)
c. A 3D PD fibroid volume being analysed using VOCAL software (bottom)

RESULTS

Patients

Of the 436 women visiting the outpatient clinic because of fibroid-related symptoms, 66 premenopausal women with a maximum of two fibroids without the use of hormonal therapy could be analysed. The majority of women already used medical therapy, had a high number of fibroids, fibroids only visible with abdominal probe, had no fibroids, were diagnosed with adenomyosis, started drug therapy or received an operation within 3 months, were post-menopausal (fewer than five women) or not willing to participate (fewer than five women). The possibility of starting medical or surgical treatment at follow up was discussed with all women. Two women used Cyklokapron (tranexamic acid) during heavy menstrual blood loss. Median fol-low up time was 11.7 months (range 2.3–28.4 months). Seven women chose therapy after 3 months of follow up, 13 women could be followed for 6–9 months and 41 were followed for 12 months or more. Twenty-seven women had more than one fibroid. Mean age was 42.8 years (SD: 7.2). Median parity was 1 (range 0–4). Mean Body Mass Index was 23.7 (SD: 3.39). Patients were referred to our outpatient clinic mostly because of possible fibroid-related symptoms; heavy menstrual bleeding 28.8%, bulk symptoms or pain 28.8%, no fibroid-related symptoms 21.2%, infertility 3% and a combination of symptoms 18.1%. Forty-seven percent of the women were north European. 15 women had 17 submucosal fibroids of which ten were FIGO PALM-COIN classification type 5 fibroids; submucosal reaching serosa.[19] Median fibroid diameter was 4.0 cm (range 1.3–8.0 cm).

Absolute fibroid volume change over 1 year

The vast majority of 3D sweeps were of sufficient or good quality (94.3%). Only in 1.4% of 3D sweeps was quality insufficient for proper VI assessment, and these were excluded, in all of these images it concerned a large fibroid. Table 1 shows descriptive information regarding various fibroid characteristics. Median fibroid volume at baseline was 20.0 cm^3 (range 6.8–92.4), at 3 months (n = 42) 29.3 cm^3 (10.4–99.5), at 6 months (n =32) 36.8 cm^3 (10.3– 113.0) and at 12 months (n = 41) 26.2 cm^3 (9.8–96.8).

Table 1. Baseline fibroid characteristics

FIBROID CHARACTERISTICS	NUMBER	FIBROID VOLUME AT BASELINE MEDIAN (RANGE*)	FIBROID VOLUME AT 12 MONTHS MEDIAN (RANGE)
All fibroids	n=66	20 (6.8-92.4)	26.2 (9.8-96.8)
Age			
≤ 35	n=12	33.9 (13.6-91.3)	9.7 (1.5-30.0)
>35	n=54	16.4 (6.6-93.4)	30.1 (11.9-140.7)
Parity			
0	n=22	16.4 (6.3-49.7)	30.1 (14.1-96.8)
≥ 1	n=44	22.3 (7.5-118.1)	16.7 (3.5-170.6)
Ethnicity			
North European	n=33	18.2 (9.4-81.6)	28.4 (10-140.7)
Other	n=33	24.2 (5.7-106.3)	26.2 (5.0-95.8)
Number of fibroids			
1	n=39	21.8 (7.1-80.9)	31.2 (12.7-163.1)
>1	n=27	16.8 (5.9-93.9)	16.7 (2.6-37.6)
Fibroid location #			
Submucosal	n=5		
Intramural	n=32	13.0 (6.4-93.9)	16.7 (6.6-36.0)
Subserosal	n=29	42.9 (10.1-120.0)	32.3 (12.1-155.7)
Diameter at baseline			
<2 cm	n=2		
2-5 cm	n=39	10.9 (5.2-18.8)	13.1 (4.3-20.1)
>5 cm	n=25	120.1 (83-150.7)	145.7 (40-258.1)
Vascular index at baseline			
Low ‡	n=34	16.8 (6.4-58.7)	14.2 (6.6-34.8)
High	n=32	29.6 (7.7-131.9)	57.3 (20.1-257.5)
VI over time			
Increased	n= 31	21.8 (9.8-57.1)	18.9 (8.3-43.5)
Unchanged	n= 10	19.9 (9.7-67.4)	21.6 (13.2-35.4)
Decreased	n=25	18.8 (6.35-123.9)	43.1 (9.6-253.6)
Fibroid volume over time ‡			
Increased	n= 28	12.2 (6.5-110.58)	25.8 (12.7-256.2)
Unchanged	n= 10	15.3 (5.2-48.2)	15.1 (3.4-45.8)
Decreased	n=28	41.5 (8.4-110.6)	29.4 (8.0-50.4)

*Interquartile range was used

‡ fibroids were categorised in fibroids which increased in volume over 1 year, stayed unchanged or decreased over 1 year

Type of fibroid was classified using the FIGO PALM-COIN classification. FIGO types 0-2 were subdivided as submucosal, type 3-5 as intramural and type 6-8 as subserosal.

¶ VI is the vascular index measured with VOCAL. The VI represents the proportion of blood vessels within the fibroid

‡ VI measured at baseline was divided into a low VI group (under the median VI at baseline) and a high VI group (above the median VI at baseline

Fibroid growth rate per year

Regarding growth rate per year we excluded three extreme values (i.e. more than 500% increase or decrease) from the analyses. The average growth rate per year was 8.98% (minimum value: 96%, maximum value: 271%). Fibroid growth rate per year was 10.5% (12.6 to 57.7%) for highly vascularised fibroids and 8.1% (51.9 to 39.3%) in fibroids with low vascularity at baseline.

Vascularisation as predictor for fibroid growth

Table 2 shows the results of the linear mixed model analyses. Although the fibroid volume distribution was skewed to the right, the residuals of the linear mixed model analyses were normally distributed so no transformation was performed. The VI ranged from 0 to 18% (proportion of blood vessels within the fibroid). VI at baseline was significantly associated with fibroid volume at 12 months, also after correction for fibroid volume at baseline. Additional adjustment for potential confounders slightly attenuated all relationships. The results indicate that an increase of 1% in VI at baseline was associated with a 7.00 cm^3 larger fibroid volume at 12 months. VI of the capsule at baseline was not significantly related to fibroid volume (Table 2). Fibroid volume at 12 months was also associated with baseline fibroid volume (crude regression coefficient 1.46, 95% CI: 1.29–1.64; $P < 0.001$; adjusted regression coefficient 1.45, 95% CI: 1.24–1.66; $P < 0.001$). After excluding an extreme value (i.e. >5 SD above the mean), VI at baseline was significantly associated with growth rate per year. The crude regression coefficient was 5.30 (95% CI: 1.82–8.95; $P = 0.04$). Adjusting for potential confounders slightly attenuated this result (adjusted regression coefficient was 4.57 (95% CI: 0.11–9.03; $P = 0.045$). In an additional analysis, VI measured at baseline was divided into a low VI group (under the median VI at base-line) and a high VI group (above the median VI at base-line). Figure 2 shows the development of fibroid volume over time for the two groups. Volume of the highly vascularised fibroids increased faster than for poorly vascularised fibroids. Besides that, we also divided baseline volume into two groups based on the median and Figure 3 shows the development of fibroid volume over time for these two groups.

Table 2. Association between fibroids Vascular Index* (VI) at baseline and capsules VI at baseline with fibroid volume over time (N=66)

VI OF THE FIBROID	CRUDE¶	P VALUE	95% CI	ADJUSTED ǂ	P VALUE	95% CI	ADJUSTED ǂǂ	P VALUE	95% CI
Overall fibroid volume	4.00	0.14	-1.33 to 9.32	3.46	0.13	-1.08 to 8.00	2.45	0.30	-2.28 to 7.18
Fibroid volume at baseline	2.04	0.47	-3.56 to 7.64	1.57	0.53	-3.31 to 6.45	0.58	0.82	-4.46 to 5.64
Fibroid volume at 3 months	4.71	0.12	-1.28 to 10.70	4.25	0.12	-1.06 to 9.56	3.39	0.22	-2.07 to 8.85
Fibroid volume at 6 months	3.25	0.34	-3.46 to 9.96	2.62	0.40	-3.50 to 8.72	1.73	0.58	-4.54 to 8.00
Fibroid volume at 12 months	7.00	**0.02**	1.06 to 12.94	6.36	**0.02**	1.09 to 1162	5.26	0.06	-0.20 to 10.73
VI of fibroid capsule	**Crude**	**P value**	**95% CI**	**Adjusted** ǂ	**P value**	**95% CI**	**Adjusted** ǂǂ	**P value**	**95% CI**
Overall fibroid volume	1.34	0.60	-3.72 to 6.40	1.76	0.42	-2.55 to 6.07	0.67	0.77	-3.81 to 5.14
Fibroid volume at 12 months #	3.69	0.22	-2.17 to 9.56	3.96	0.14	-12.7 to 9.19	2.71	0.32	-2.71 to 8.13

*Vascular Index (VI) is the number of colour voxels divided by the total number of both colour and grey voxels, representing the proportion of blood vessels within the tissue (fibroid or fibroids capsule)

** Fibroid volume and VI was measured with VOCAL software; After fibroid volume acquisition using the manual contour mode and for the capsule the shell mode, VI was automatically calculated with the "histogram" function.

¶Analyses were performed using linear mixed model analysis for repeated measurements. Crude and adjusted regression coefficients are listed (with their corresponding p values and 95% confidence intervals), N=66

ǂAdjusted for fibroid volume at baseline

ǂǂ Additionally adjusted for age, parity, race, fibroid location and number of fibroids

At baseline, 3 and 6 months there was also no significant association

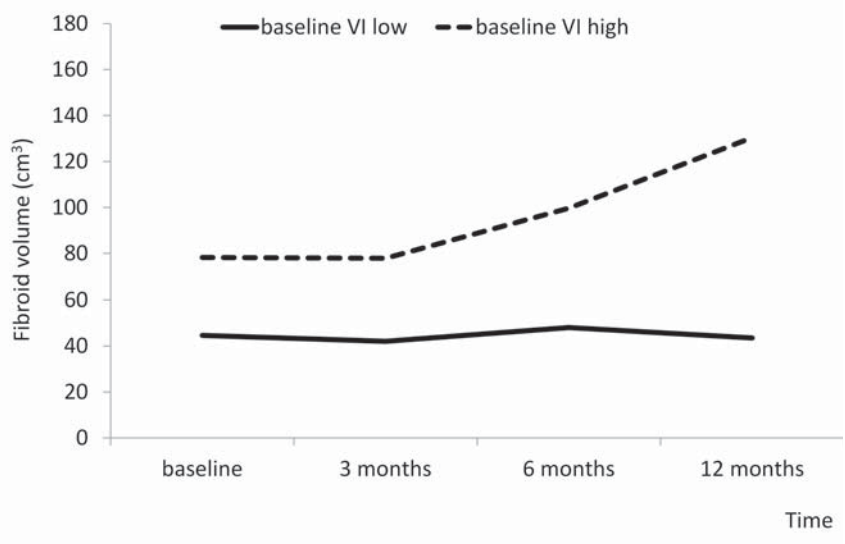


Figure 2. Relation fibroid vascularisation and fibroid growth. * Vascular Index (VI) is the number of colour voxels divided by the total number of both colour and grey voxels, representing the proportion of blood vessels within the tissue. ** VI was measured with 3D power Doppler ultrasound and calculated with VOCAL software. After fibroid volume acquisition (using the manual contour mode),VI was automatically calculated with the "histogram" function. *** VI measured at baseline was split into a low VI-group; VI under the median VI at baseline and a high VI-group; VI above the median VI at baseline. Total group N=66. In the mixed model analyses, vascularisation was significantly correlated with fibroid growth, even when we corrected for fibroid volume (not performed in figure).

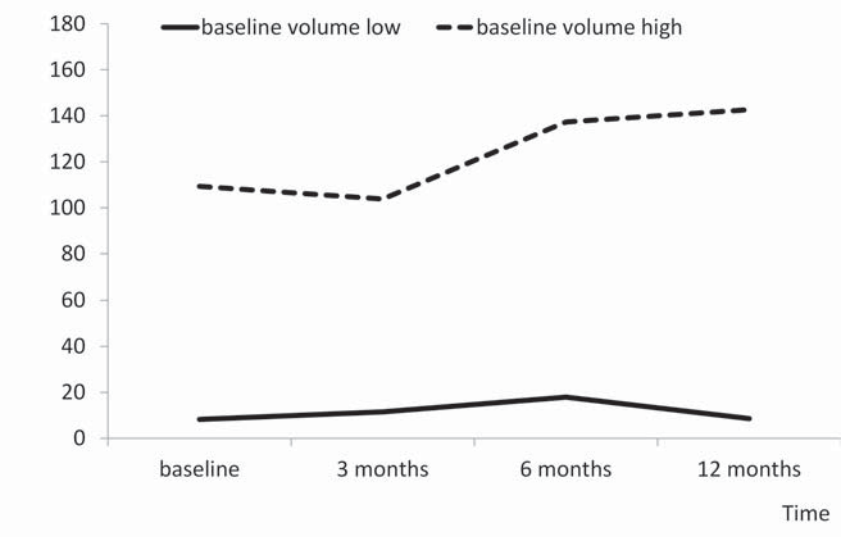


Figure 3. Relation fibroid volume at baseline and fibroid growth

DISCUSSION

Main findings

Baseline fibroid vascularisation measured with 3D PD was significantly related to fibroid volume at 12 months and fibroid growth rate as a % of volume at baseline over 1 year. Fibroid volume increase was larger in highly vascularised fibroids (also after correction for baseline fibroid volume and other confounders). VI of the fibroid capsule at baseline was not related to fibroid volume at 12 months.

Strengths and limitations

Patient selection was carefully designed to obtain a homogeneous group of patients and to observe natural behaviour of fibroids. Patients included had a maximum of two fibroids to allow proper follow up of fibroid measurements and were all included consecutively to reduce the risk of selection bias. Since attenuation can effect 3D PD,[20] a maximum fibroid size of 8 cm was chosen to avoid large affects due to attenuation. Still, it cannot be excluded that some fibroids could have been erroneously classified into the low or high VI group. On the other hand, only five fibroids were 8 cm in largest diameter and in only 1% of the 3D volumes could VI not be calculated due to poor quality. Before the present study was conducted we defined our optimal method for volume and VI assessment and demonstrated our method for measuring fibroid volume

and used vascular indices to be highly reproducible in fibroids.[14] We were able to follow up 88.5% of our patients at 1 year and all repeated measurements were executed by the same sonographer on the same machine using the same settings. Another strength is that we adjusted for potential con-founders; fibroid volume at baseline, age, parity, race, fibroid location and number of fibroids. Due to the limited sample size we were not able to correct for many other potential confounding factors such as smoking habits or diet.[21,22] We did not evaluate fibroid localisation in relation to the large uterine vessels. This could also be interesting in the future. Given the fact that we included a selective group of women without therapy and with a limited number of fibroids, our data cannot be extrapolated to women receiving therapy or with an extensive number of fibroids. Also, this group of women might be relatively asymptomatic as they have not chosen medical or surgical treatment over these 12 months.

Interpretation

Angiogenesis and vascularisation are considered crucial factors in fibroid development and growth.[9,23] Several studies using contrast magnetic resonance imaging reported a reduced blood flow in fibroids compared to its surrounding myometrium.[24,25] Differences between uteri with and without fibroids have been studied using 2D colour Doppler. Fibroid uteri showed an increased blood velocity, a decreased resistance index and a decreased pulsatility index in their uterine arteries.[26,27] Fibroid vascularisation has been compared to its surrounding myometrium and fibroid growth has been followed over time;[7,21] however, only a few studies reported on both vascularisation and growth in fibroids.[28,29] Tsuda et al.[30] studied fibroid volume and colour Doppler and reported a correlation between a low uterine artery pulsatility index and growth. A low uterine artery pulsatility index suggests greater blood flow to the fibroid facilitating growth and resulting in more vascularised fibroids. A few studies assessed fibroid volume and VIs after treatment. Czuczwar et al.[16] reported a decrease in fibroid volume and VIs after 3 months of ulipristal ther-apy. In the study by Chia et al.[15] 2 months of gonadotrophin-releasing hormone analogue therapy did not change vascular indices (21 women), while fibroid volume decreased. Using 3D power Doppler ultrasound the present study confirmed the association between vascularisation of the fibroid and fibroid growth. Methods of recording a 3D PD volume, calculating fibroid volume and vascular assessment were similar in the present study as reported in other studies.[13–16] In 3D PD there are several factors influencing PD indices which should be considered. VI results are dependent on distance between the examined tissue and the probe,[31] which is a basic limitation of the method. Several techniques like spatio-temporal image correlation high-definition flow technology and fractional moving blood volume are reported to minimise this effect.[19,32,33] Another influence on PD indices reported is the

cardiac cycle, which may vary between systole and diastole.[30,34–36] In fibroids this could not be confirmed (Nieuwenhuis et al, submitted). The capsule of the fibroid surrounds the fibroid and at the same time can be seen as a different entity. It has been a subject of interest and has been studied from different perspectives using different techniques (histopathological, immunohistochemical, [angiogenic] gene expression, growth factors, neurotransmitters, imaging techniques).[9–12,23,37,38] In this study no correlation was found between fibroid capsule vascularisation and fibroid growth. An explanation might be that most fibroids have a vascular capsule and therefore it is less discriminative as a predictor for fibroid growth. Another explanation can be that the capsule is more comparable to the surrounding myometrium than to the fibroid.[39] To our knowledge the capsule has never been studied with 3D PD ultrasound in relation to growth.

Several studies followed women with fibroids over time and reported about fibroid growth (rate).[5–7,30] Our results are similar to these studies. All studies demonstrate that fibroids can spontaneously decrease or grow over time. Growth rates in our study are comparable to those found by Peddada et al.[7] They compared fibroid growth rate in black women and white women and reported that the only factor affecting growth rate was the number of fibroids, which is similar to our result; solitary fibroids tend to grow faster than multiple ones. Mavrelos et al.[6] found type of fibroid to be of influence on growth rate. Intramural fibroids grew faster than subserosal and submucosal fibroids, we found similar results. They also found that fibroids <2 cm grew faster than larger ones. Age, parity and number of fibroids were not of influence. Unexpectedly, we found in women aged <35 years that the majority of fibroids decreased over time; however, this was not corrected for possible confounders, possibly these were, for example, mainly smaller fibroids in this age group. We found, besides vascularisation, size at presentation and number of fibroids to be of influence on fibroid growth rate.

CONCLUSION

The current study underlines our hypothesis that highly vascularised fibroids tend to grow faster than poorly vascularised fibroids. Determining the growth potential of an individual fibroid will benefit clinical decision making. Our conclusions are limited to women with fibroids <8cm not receiving therapy. The included group of women with limited symptoms and with small to intermediate fibroids is a challenging group as we do not know whether it is beneficial to offer these women therapy or not. This depends on the growth potential of fibroids. When growth potential is high, follow up is needed and therapy could be considered to prevent larger fibroids that are less likely to be treatable by minimally invasive options. However, if the growth potential is low,

unnecessary therapies could be prevented and follow up could be diminished. Our results should be confirmed in future studies, preferably with longer follow up, and clear cut-off levels need to be established before the current technique can be implemented in daily practice. Besides the potential of predicting growth, 3D PD may also be useful in predicting the effect of hormonal or minimally invasive therapy but this needs to be established in future studies. The same accounts for 3D PD evaluation in the prediction of the effectiveness of minimally invasive techniques.[40–43] Given the lower costs and better accessibility of 3D PD compared with magnetic resonance imaging, 3D PD can be seen as having strong potential for implementation in clinical practice provided that future studies confirm the current results. In conclusion, baseline vascularisation (VI) measured with 3D PD was associated with fibroid volume at 12 months and with fibroid growth rate per year.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Details of ethics approval

The study was approved by the VUmc Medical Ethical Committee on 8-3-2012, number 2012/092.

Funding

None.

Acknowledgements

Special thanks to K. Demissi and C. Nikkels for their help with completing the database.

REFERENCES

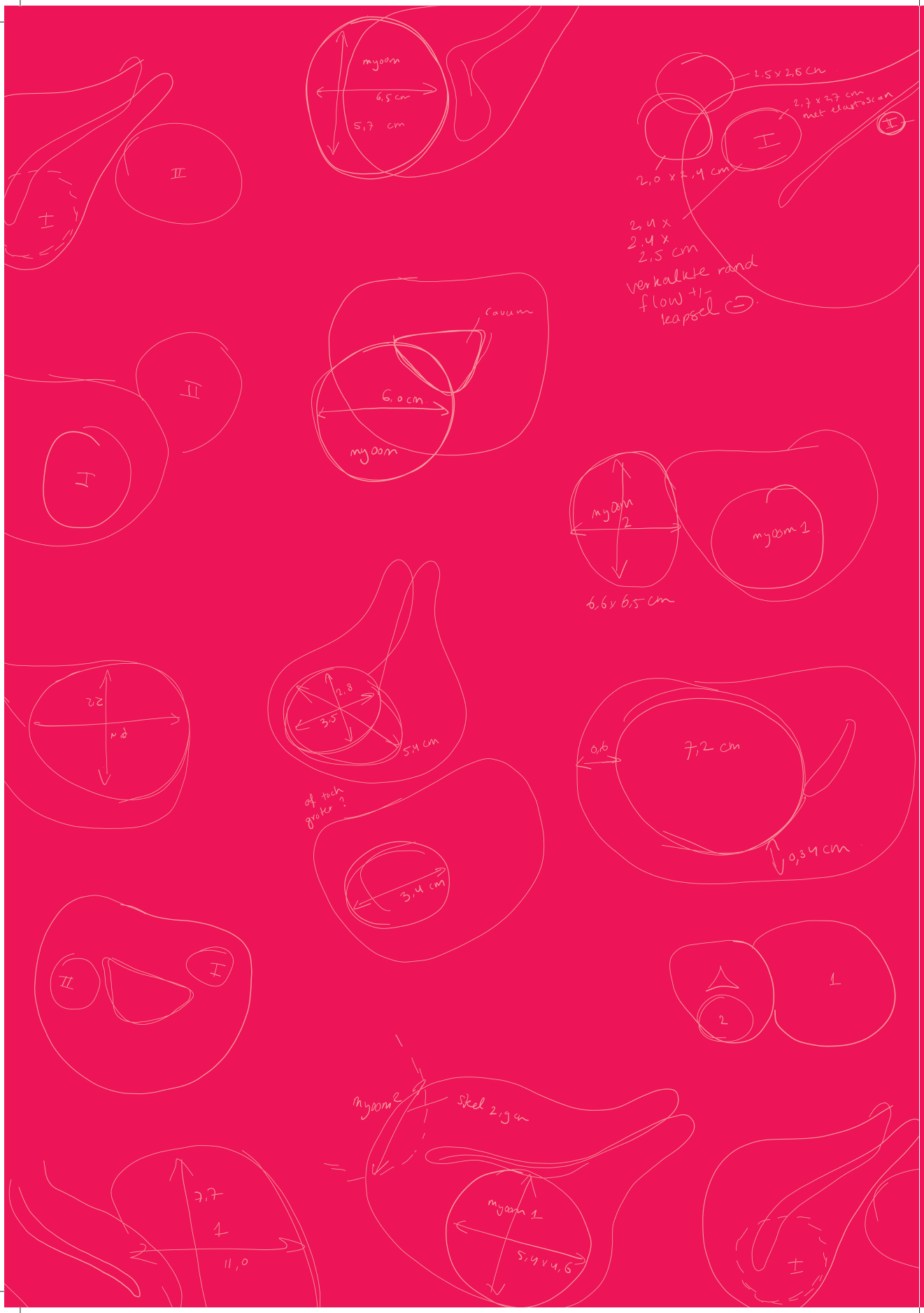
1. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012 Mar;206(3):211 e1-9.
2. Downes E, Sikirica V, Gilabert-Estelles J, Bolge SC, Dodd SL, Maroulis C, et al. The burden of uterine fibroids in five European countries. Eur J Obstet Gynecol Reprod Biol. 2010 9/2010;152(1):96-102.
3. Fernandez H, Farrugia M, Jones SE, Mauskopf JA, Oppelt P, Subramanian D. Rate, type, and cost of invasive interventions for uterine myomas in Germany, France, and England. J Minim Invasive Gynecol. 2009 1/2009;16(1):40-6.
4. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect. 2003 Jun;111(8):1037-54.
5. DeWaay DJ, Syrop CH, Nygaard IE, Davis WA, Van Voorhis BJ. Natural history of uterine polyps and leiomyomata. Obstet Gynecol. 2002 2002;100(1):3-7.
6. Mavrelos D, Ben-Nagi J, Holland T, Hoo W, Naftalin J, Jurkovic D. The natural history of fibroids. Ultrasound Obstet Gynecol. 2010 Feb;35(2):238-42.
7. Peddada SD, Laughlin SK, Miner K, Guyon JP, Haneke K, Vahdat HL, et al. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci U S A. 2008 12/16/2008;105(50):19887-92.
8. Baird DD, Garrett TA, Laughlin SK, Davis B, Semelka RC, Peddada SD. Short-term change in growth of uterine leiomyoma: tumor growth spurts. Fertil Steril. 2011 Jan;95(1):242-6.
9. Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update. 2014 Mar-Apr;20(2):194-216.
10. Di Tommaso S, Massari S, Malvasi A, Bozzetti MP, Tinelli A. Gene expression analysis reveals an angiogenic profile in uterine leiomyoma pseudocapsule. Mol Hum Reprod. 2013 Jun;19(6):380-7.
11. Tinelli A, Malvasi A, Rahimi S, Negro R, Cavallotti C, Vergara D, et al. Myoma pseudocapsule: a distinct endocrino-anatomical entity in gynecological surgery. Gynecol Endocrinol. 2009 10/2009;25(10):661-7.
12. Walocha JA, Litwin JA, Miodonski AJ. Vascular system of intramural leiomyomata revealed by corrosion casting and scanning electron microscopy. Hum Reprod. 2003 5/2003;18(5):1088-93.
13. Minsart AF, Ntoutoume SF, VAndenhoute K, Jani J, Van PC. Does three-dimensional power Doppler ultrasound predict histopathological findings of uterine fibroids? A preliminary study. Ultrasound Obstet Gynecol. 2012 12/2012;40(6):714-20.
14. Nieuwenhuis LL, Betjes HE, Hehenkamp WJ, Heymans MW, Brolmann HA, Huirne JA. The use of 3D power Doppler ultrasound in the quantification of blood vessels in uterine fibroids: feasibility and reproducibility. J Clin Ultrasound. 2015 3/2015;43(3):171-8.

15. Chia CC, Huang SC, Chen SS, Kang JY, Lin JC, Lin YS, et al. Ultrasonographic evaluation of the change in uterine fibroids induced by treatment with a GnRH analog. Taiwan J Obstet Gynecol. 2006 6/2006;45(2):124-8.
16. Czuczwar P, Wozniak S, Szkodziak P, Milart P, Wozniakowska E, Wrona W, et al. Influence of ulipristal acetate therapy compared with uterine artery embolization on fibroid volume and vascularity indices assessed by three-dimensional ultrasound: prospective observational study. Ultrasound Obstet Gynecol. 2015 6/2015;45(6):744-50.
17. Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS, Perkins A, et al. Evaluation of the effect of machine settings on quantitative three-dimensional power Doppler angiography: an in-vitro flow phantom experiment. Ultrasound Obstet Gynecol. 2008 9/2008;32(4):551-9.
18. Collins SL, Stevenson GN, Noble JA, Impey L, Welsh AW. Influence of power Doppler gain setting on Virtual Organ Computer-aided AnaLysis indices in vivo: can use of the individual sub-noise gain level optimize information? Ultrasound Obstet Gynecol. 2012 7/2012;40(1):75-80.
19. Munro MG, Critchley HO, Broder MS. Fraser, IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011;113:3–13.
20. Miyague AH, Raine-Fenning NJ, Polanski L, Martinez LH, Araujo JE, Pavan TZ, et al. Assessing repeatability of 3D Doppler indices obtained by static 3D and STIC power Doppler: a combined in-vivo/in-vitro flow phantom study. Ultrasound Obstet Gynecol. 2013 11/2013;42(5):571-6.
21. Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril. 2007 Apr;87(4):725-36.
22. Parazzini F, Di Martino M, Candiani M, Vigano P. Dietary components and uterine leiomyomas: a review of published data. Nutr Cancer. 2015;67(4):569-79.
23. Fleischer R, Weston GC, Vollenhoven BJ, Rogers PA. Pathophysiology of fibroid disease: angiogenesis and regulation of smooth muscle proliferation. Best Pract Res Clin Obstet Gynaecol. 2008 8/2008;22(4):603-14.
24. Forssman L. Blood flow in myomatous uteri as measured by intra-arterial 133Xenon. Acta Obstet Gynecol Scand. 1976;55(1):21-4.
25. Forssman L. Distribution of blood flow in myomatous uteri as measured by locally injected 133Xenon. Acta Obstet Gynecol Scand 1976;55:101–4.
26. Sladkevicius P, Valentin L, Marsal K. Transvaginal Doppler examination of uteri with myomas. J Clin Ultrasound 1996;24:135–40.
27. Kurjak A, Kupesic-Urek S, Miric D. The assessment of benign uterine tumor vascularization by transvaginal color Doppler. Ultrasound Med Biol 1992;18:645–9.
28. Alatas G, Aksoy E, Akarsu C, Yakin K, Bahceci M. The effect of uterine volume on uterine artery Doppler velocimetry in the myomatous state. Gynecol Obstet Invest 1997;43:55–9.

29. Huang SC, Yu CH, Huang RT, Hsu KF, Tsai YC, Chou CY. Intratumoral blood flow in uterine myoma correlated with a lower tumor size and volume, but not correlated with cell proliferation or angiogenesis. Obstet Gynecol 1996;87:1019–24.
30. Tsuda H, Kawabata M, Nakamoto O, Yamamoto K. Clinical predictors in the natural history of uterine leiomyoma: preliminary study. J Ultrasound Med 1998;17:17–20.
31. Miyague AH, Pavan TZ, Grillo FW, Teixeira DM, Nastri CO, Martins WP. Influence of attenuation on three-dimensional power Doppler indices and STIC volumetric pulsatility index: a flow phantom experiment. Ultrasound Obstet Gynecol 2014;43:103–5.
32. Soares CA, Miyague AH, Filho FM, Raine-Fenning N, Martins WP. Fractional moving blood volume (FMBV) concept can be applied to 3D power Doppler quantification. Ultrasound Obstet Gynecol 2013;41:98–9.
33. Stevenson GN, Collins SL, Welsh AW, Impey LW, Noble JA. A technique for the estimation of fractional moving blood volume by using three-dimensional power Doppler US. Radiology 2015;274:230–7.
34. Martins WP, Raine-Fenning NJ, Ferriani RA, Nastri CO. Quantitative three-dimensional power Doppler angiography: a flow-free phantom experiment to evaluate the relationship between color gain, depth and signal artifact. Ultrasound Obstet Gynecol 2010; 35:361–8.
35. Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS, Perkins A, et al. Determining the relationship between threedimensional power Doppler data and true blood flow characteristics: an in-vitro flow phantom experiment. Ultrasound Obstet Gynecol 2008;32:540–50.
36. Welsh A, Hou M, Meriki N, Stevenson G. Use of four-dimensional analysis of power Doppler perfusion indices to demonstrate cardiac cycle pulsatility in fetoplacental flow. Ultrasound Med Biol 2012;38:1345–51.
37. Tinelli A, Mynbaev OA, Mettler L, Hurst BS, Pellegrino M, Nicolardi G, et al. A combined ultrasound and histologic approach for analysis of uterine fibroid pseudocapsule thickness. Reprod Sci 2014;21:1177–86.
38. Tsiligiannis SE, Zaitseva M, Coombs PR, Shekleton P, Olshansky M, Hickey M, et al. Fibroid-associated heavy menstrual bleeding: correlation between clinical features, Doppler ultrasound assessment of vasculature, and tissue gene expression profiles. Reprod Sci 2013;20:361–70.
39. Malvasi A, Cavallotti C, Morroni M, Lorenzi T, Dell'Edera D, Nicolardi G, et al. Uterine fibroid pseudocapsule studied by transmission electron microscopy. Eur J Obstet Gynecol Reprod Biol 2012;162:187–91.
40. deSouza N, Williams A. Uterine arterial embolization for leiomyomas: perfusion and volume changes at MR imaging and relation to clinical outcome. Radiology 2002;222:367–74.
41. Isonishi S, Coleman RL, Hirama M. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. Am J Obstet Gynecol 2008;198:270 e1.

42. Yoon SW, Lee C, Kim KA, Kim SH. Contrast-enhanced dynamic MR imaging of uterine fibroids as a potential predictor of patient eligibility for mr guided focused ultrasound (MRgFUS) treatment for symptomatic uterine fibroids. Obstet Gynecol Int 2010;2010:pii:834275.

43. Funaki F, Fukunishi H, Funaki T, Sawada K, Kaji Y, Maruo T. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. Am J Obstet Gynecol 2007;196:e1–6.


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

09

Fibroid vascularisation assessed with 3D power Doppler as predictor for fibroid related symptoms and quality of life: a prospective cohort study

A.L. Keizer
L.L. Nieuwenhuis
W.J.K. Hehenkamp
J.W.R. Twisk
H.A.M. Brölmann
J.A.F. Huirne

Submitted BJOG august 2017

ABSTRACT

Objective: To investigate the association between fibroid vascularisation, using 3D PD parameters, and heavy menstrual bleeding, fibroid related symptoms and quality of life.

Design: prospective cohort study

Setting: outpatient clinic of the VU medical centre, Amsterdam

Population: premenopausal women diagnosed with a maximum of 2 fibroids whom chose expectant management

Method: 3D sonography including Power Doppler was performed at baseline, 3, 6 and 12 months follow up. Participants were asked to complete PBAC and UFS-QOL questionnaires at baseline and after 3, 6 and 12 months of follow-up.

Main outcome measures: Linear mixed model analyses for repeated measurements were applied to analyse baseline fibroid vascularisation and baseline fibroid volume in relation to fibroid related symptoms (PBAC, symptoms and health related quality of life) over one year of follow up.

Results: Baseline fibroid vascularisation (vascular index) is associated with PBAC score over time; a 1% higher VI at baseline leads to an 14.6 point increase in PBAC score (p=0.04; 95% CI 0.62 – 28.46). When adjusted for fibroid volume at baseline and type of fibroid association was not significant. Fibroid volume at baseline and heavy menstrual bleeding over time are associated (p=0.03, 95% CI 0.05 – 1.07).

Conclusions: This study showed that both fibroid vascularisation and fibroid volume are associated with an increase of the amount of menstrual blood loss and fibroid related symptoms over time and quality of life.

Funding: none

Keywords: Uterine fibroid, 3D, Power Doppler, Vascularity, Heavy Menstrual Bleeding, Health Related Quality of Life

Tweetable abstract: fibroid vascularisation and fibroid volume are associated with an increase of fibroid related symptoms over time

INTRODUCTION

Uterine fibroids may cause morbidity and affect quality of life [1]. Fibroids are associated with heavy menstrual bleeding, though not all fibroids cause heavy menstrual bleeding [2]. There is no consistent relationship between the size and location of fibroids and heavy menstrual bleeding [1]. It has been reported that uterine fibroids are asymptomatic in at least 50% of the afflicted women. Contrarily, heavy menstrual bleeding occurs in up to 30% of the symptomatic women [3]. Other clinical symptoms are dysmenorrhea, (noncyclic) pelvic pain, bulk symptoms, like altered urinary frequency and defecation pattern, and problems with reproduction [3;4].

Heavy menstrual bleeding and reproductive problems are related to the level of distortion of the uterine cavity, i.e. are more frequent in case of submucous fibroids [5-7]. According to the FIGO PALM COEIN classification submucous fibroids are types 0,1,2 and 3, intramural fibroids type 4 and subserosal fibroids types 5, 6 and 7. Fibroids that impact both endometrium and serosa are classified as type 2-5 [8]. Fibroids have various levels of degeneration, from well vascularized up to calcified non-vascularized. Vascularisation has been reported to be a predictor for fibroid growth [9]. We hypothesize that besides the localisation of fibroids also size and vascularisation affect abnormal bleeding. We expect that well vascularized submucosal or intramural fibroids (FIGO type 0 - 4 and 2-5) will induce heavier bleeding than for example the same type of fibroids that are calcified or degenerated without any vessels. We expect vascularity will not affect the bleeding pattern in case of subserosal fibroids (type 5,6 or 7). We hypothesise that symptoms in women with well vascularized fibroids will increase over time while symptoms in degenerated fibroids will remain the same or decrease. Additionally we hypothesise that fibroids size at baseline is associated with symptoms increase over time.

3D Power Doppler (3D PD) is reported to be a reproducible technique in the assessment of uterine fibroids volume and in the quantification of its vascularity [9-11]. Only a few previous studies used 3D PD in the assessment of symptomatic fibroids [12-15]. Determining vascularisation and thereby possibly predicting which fibroids will potentially give more complaints over time, could have implications for counselling patients about therapeutic options for relief of symptoms. Therefore our aim is to study the association between fibroid vascularisation and volume, quantified by 3D Power Doppler, and heavy menstrual bleeding, with other fibroid related symptoms and quality of life and their change over time.

METHODS

Study design

A prospective cohort study was performed between March 2012 and March 2014 at our outpatient clinic, department of gynaecology and obstetrics, VU medical centre (tertiary referral centre), Amsterdam. All women diagnosed with a maximum of 2 fibroids without the use of hormonal drug therapy were consecutively asked to participate and included. Exclusion criteria were fibroids larger than visible with a vaginal probe (in general > 8cm), more than 2 fibroids at baseline, adenomyosis, pregnancy and hormonal or surgical therapy planned/started within 12 months. A maximum of 2 fibroids at baseline was chosen to avoid any risk of mixing measurements of the fibroids in the same patient during follow up, women with additional fibroids discovered during follow-up were not excluded.

We performed ultrasonography and patients completed PBAC scores and UFS-QOL questionnaires at baseline and after 3, 6 and 12 months of follow up. The study was listed in the Dutch Trial Register; number NTR3349 and approved by the ethical board of the VUmc.

We studied the association between fibroid vascularisation (VI) at baseline and change over time of the amount of menstrual bleeding (PBAC score) and other fibroid related symptoms and fibroid related quality of life (UFS-QOL scores) during one year follow-up. We also studied the association between VI at baseline and PBAC, UFS and UFSQOL at baseline and PBAC, UFS and UFSQOL at 12 months of follow-up).

Secondly, we performed the same analyses for fibroid volume at baseline and change of symptoms over time and at a single measurement point (baseline and 12 months).

Ultrasound & machine settings

2D sonography (at baseline and after 3, 6 and 12 months of follow-up) and 3D sonography including Power Doppler (at baseline) were performed using the Accuvix V10 ultrasound machine (Samsung-Medison, Seoul, South Korea). Gel infusion sonography (GIS) was performed in case of uncertainty regarding fibroid type. All volumes were acquired by an experienced examiner (LLN) in a standardised way using a 3D vaginal probe (5-8 MHz) as previously published to result in the best reproducibility [10;11;16;17]. Power Doppler settings were set to at a fixed Gain at 50dB, Frequency 5-8 MHz, pulse repetition frequency 0.60 kHz, and wall motion filter low. Size, location, FIGO classification and subjective impression of vascularisation of the fibroid were noted. A 3D PD volume was

taken to assess fibroids volume and vascular parameters. Fibroids locations and sizes were also drawn schematically to ensure correct follow up of the same fibroids over time.

Off-line evaluation of the 3D Volumes

All stored volumes were evaluated with VOCAL software, Sonoview Pro- 1.6.2. (Samsung-Medison, Seoul, South Korea). 3D sweep quality was scored 1 to 5 on a Likert scale for different US entities (1. contrast, sharpness, brightness, 2. visibility of fibroid (border), 3. penetration depth, 4. total fibroid visible in sweep, 5. movement artefacts). Volume and Vascular Index (VI) were calculated using the manual contour mode in VOCAL (Virtual Organ Computer-aided AnaLysis). Fibroid contours were drawn in six consecutive planes using a 30° rotation step. Power Doppler indices were then automatically calculated using the histogram function. Fibroid contours measured did not contain its capsule. The fibroid capsule was measured separately [10]. The VI represents the proportion of blood vessels within the tissue (number of colour voxels divided by the total number of both colour and grey voxels). See figure 1.

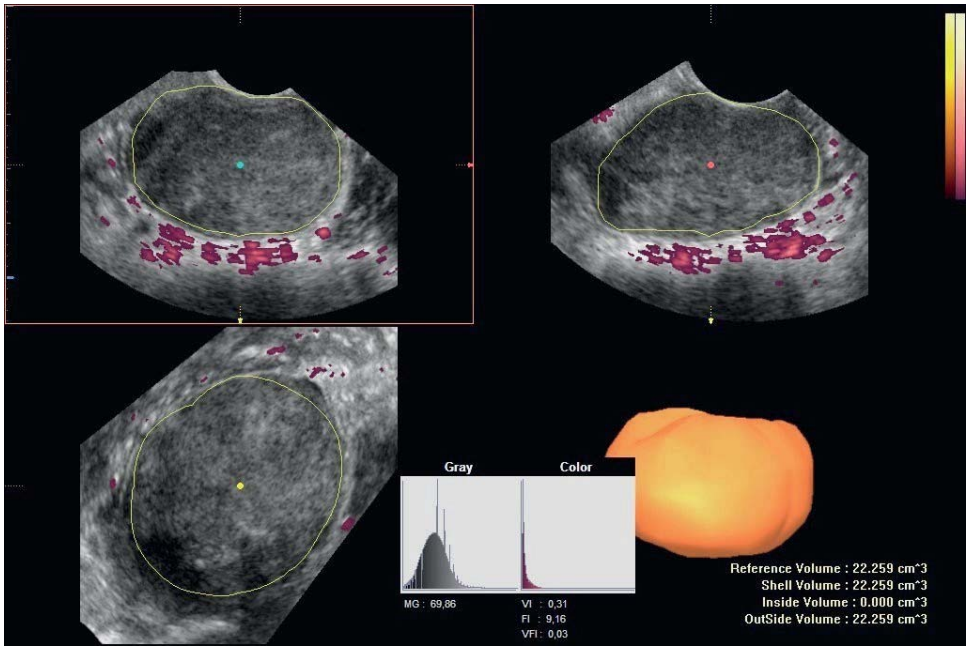


Figure 1. Offline analysis of Power Doppler indices, automatically calculated using the histogram function.

Questionnaires

Patients were asked to fill out a pictorial blood assessment chart (PBAC) to quantify menstrual blood loss [18-23] and Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL) [24] at baseline and after 3, 6 and 12 months of follow up. A PBAC score of ≥150 was considered heavy menstrual bleeding [20-22].The UFS-QOL symptom score is based on complaints of abnormal and heavy menstrual bleeding as well as bulky symptoms. UFS-QOL symptom scores range from 0-100 (0 meaning no symptoms) and UFS-QOL quality of life scores range from 0-100 (100 meaning best possible quality of life).

Statistical analysis

All analyses were performed using IBM SPSS Statistics 23.0 software package (IBM, New York, NY, USA). Linear mixed model analyses for repeated measurements were applied to analyse baseline fibroid vascularisation in relation to fibroid related symptoms (PBAC, symptoms and health related quality of life) over one year of follow up. Analyses were adjusted for fibroid volume at baseline and secondly for race, fibroid type and number of fibroids. Secondly the relationship between fibroid volume at baseline and fibroid related symptoms over one year follow up was studied the same way. A $p<0.05$ was considered statistically significant. Linear regression was used for subgroup analyses; they were performed for type of fibroid. We defined 3 groups; submucous (FIGO type 0 - 3 and type 2-5), intramural (FIGO type 4) and subserosal (FIGO type 5 - 7) and number of fibroids (1 vs ≥2). The subgroup of submucous fibroids was defined as all women having at least one submucous fibroid.

RESULTS

Patient characteristics

66 women with a maximum of two fibroids without the use of hormonal drug therapy were followed for 12 months. In total 53 women (80%) completed one or more PBAC or UFS-QOL questionnaires and could be included in our analyses. For patient characteristics see table 1. For fibroid characteristics see table 2.

PBAC score

Of the 53 women who filled out a questionnaire, 47 (88.7%) filled out one or more PBAC's.

Table 1

PATIENT CHARACTERISTICS		
Age (mean, SD)	43.40 (7.16)	
Race	European	52.9%
	African	15.1%
	South-American	15.1%
	Asian	13.2%
	Other	3.8%
Parity	Mean 1.08 (SD 1.02)	
Number of fibroids	1 fibroid	29 (55%)
	≥2 fibroids	24 (45%)
Presenting symptom	Heavy bleeding	32.1%
	Pain	18.9%
	Bulk symptoms	7.5%
	Fertility problems	3.8%
	Combination	18.9%
	No complaints	18.9%

Table 2

FIBROID CHARACTERISTICS AND QUESTIONNAIRES		
Number of fibroids	1	27 (50.9%)
	(>)2	26 (49.1%)
Single fibroids	*Largest diameter < 5cm	20 (74,1%)
	Largest diameter > 5cm	7 (25,9%)
	Type	Submucous 4 (14.8%)
		Intramural 9 (33.3%)
		Subserosal 14 (51.9%)
Two fibroids	Largest diameter < 5cm	12 (46.2%)
	Largest diameter > 5cm	14 (53.8%)
	Type **	Submucous 3 (11.5%)
		Intramural 17 (65.4%)
		Subserosal 6 (23.1%)

*Largest diameter of the largest fibroid

**Type of most protruding fibroid

Thirty four women (72.3%) scored ≥150 at least once. Of the women with 1 fibroid, 17 (68.0%) scored ≥150 at least once and of the women with multiple fibroids, 17 (77.3%) women scored ≥150 at least once. 13 women (27.7%) consistently scored <150 on more PBAC's.

Median PBAC score for submucous fibroids was 269 (range 12-750), for intramural fibroids (FIGO type 4) 181 (range 0-783) and subserosal fibroids 152 (range 0-468).

Questionnaires; fibroid related symptoms and quality of life

53 women (100%) filled out one or more UFS-QOL questionnaires. Mean symptom score at baseline was 41.9 out of 100 (SD 19.8), for women with 1 fibroid it was 45.1 (SD 16.2) and for women with multiple fibroids it was 38.8 (SD 22.7). For submucous fibroids median score was 32.8 (0-81), for intramural fibroids 43.8 (19-76) and for subserosal fibroids 43.8 (16-75). Mean quality of life score at baseline was 62.7 out of 100 (SD 19.1), for women with 1 fibroid it was 58.1 (SD 15.8) and for women with multiple fibroids it was 67.6 (SD 21.3). For submucous fibroids median score was 67,7 (43-100), for intramural fibroids 56.5 (32-91) and for subserosal fibroids 65.52 (19-100).

Fibroid vascularisation and abnormal uterine bleeding

The association between baseline vascularisation and bleeding symptoms over time (repeated measurements analysis) showed that a 1% higher VI at baseline resulted in an 14.6 point higher PBAC score over time (p=0.04, 95% CI 0.62 – 28.46). If we adjust for race and number of fibroids this association is still statistically significant. If we also adjust for fibroid volume at baseline and type of fibroid association is not significant (p=0.54, regression coefficient -9.8, 95% CI -42.5 to 22.84). VI at baseline and PBAC score (both at baseline and at 12 months) showed no statistically significant association (p=0.82 and p= 0.36 respectively). Subgroups analyses for type of fibroid (submucous, intramural and subserosal) showed a statistically significant association between baseline VI and PBAC score at 12 months follow up for intramural fibroids (regression coefficient 15.4; p= 0.004; 95% CI 6.8-24.0).

Fibroid vascularisation and fibroid related symptoms and health related quality of life

The association between baseline VI and UFS-QOL scores during 12 months follow up (repeated measurements analysis) were not statistically significant, UFS-QOL symptom score (regression coefficient 0.7; p=0.2 ; 95% CI -0.38 to 1.79) and UFS-QOL quality of life (regression coefficient -0.51; p=0.37 ; 95% CI -1.7 to 6.29). No association was found

for baseline VI and UFS-QOL symptom score at baseline and 12 months (p=0.97 and p= 0.62 respectively) or baseline and 12 months UFS-QOL quality of life score (p=0.9 and p= 0.87 respectively). Subgroup analyses showed also no association, see table 3.

Table 3. Relation baseline VI and fibroid related symptoms at baseline and at 12 months of follow up

		AT BASELINE				AT 12 MONTHS FOLLOW UP			
		N	RC*	P-VALUE	95% CI*	N	RC*	P-VALUE	95% CI*
PBAC	*Submucous*	10/16	-21.5	0.3	-67 to 24.2	5/16	51.4	0.88	-1018 to 1121
	Intramural	9/16	9.8	0.5	-27.6 to 47.2	9/16	15.4	0.004	6.8 to 24.0
	Subserosal	12/21	-15.5	0.41	-55.9 to 24.9	7/21	3.7	0.9	-70.9 to 78.3
UFS QOL	Submucous	14/16	-0.3	0.8	-2.8 to 2.5	6/16	-36.2	0.46	-161.9 to 89.6
	Intramural	13/16	1.2	0.33	-1.3 to 3.6	9/16	0.15	0.91	-2.7 to 2.9
	Subserosal	14/21	-0.11	0.91	-2.3 to 2.1	8/21	-9.6	0.26	-28.5 to 9.4
UFS QOL -HRQOL	*Submucous*	14/16	0.29	0.77	53.3 to 82.3	6/16	37.6	0.35	-24.3 to 130.6
	Intramural	12/16	0.14	0.90	-2.2 to 2.5	9/16	-0.15	0.93	-4.15 to 3.8
	Subserosal	13/21	-1.17	0.34	-3.8 to 1.45	7/21	0.007	0.99	-26.6 to 26.8

*regression coefficient

** CI= confidence interval

Classification: Submucous= FIGO type 0- 3 and type 2-5, Intramural = FIGO type 4, Subserosal = FIGO type 5-7

Fibroid volume and abnormal uterine bleeding

Fibroid volume at baseline and heavy menstrual bleeding over time are associated; a 10 cm^3 larger fibroid volume at baseline is associated with a 5.6 point higher PBAC score over time (p=0.03, 95% CI 0.05 – 1.07). This association was still significant when adjusted for type and number of fibroids and race. If adjusted for fibroid vascularisation at baseline, association was not significant (regression coefficient 3.2; p= 0.25; 95% CI -0.22 to 0.86). No association was found for baseline volume and PBAC score at baseline or 12 months (p=0.24 and p= 0.07 respectively). In subgroup analyses intramural fibroids showed a significant association between fibroid volume at baseline and PBAC score at 12 months (regression coefficient 1.42; p=0.0001; 95% CI 0.79-2.05).

Fibroid volume and fibroid related symptoms and health related quality of life

A 10 cm^3 larger fibroid volume at baseline is associated with a 0.57 higher UFS-QOL symptom score (scale 0-100) on average over time (p=0.03, 95% CI 0.01 – 0.11). Also no association was found for baseline volume and baseline UFS-QOL symptom score (p=0.83) or UFS-QOL quality of life score (p=0.71). Subgroup analyses showed a significant association for intramural fibroids between baseline fibroid volume and UFS-QOL symptom score at 12 months (regression coefficient 0.18; p= 0.003; 95% CI 0.08-0.29).

Number of fibroids

Women with 2 fibroids at baseline noted on average a 10 point higher UFS-QOL quality of life score over time than women with 1 fibroid at baseline (95% CI 1.79 -17.88 p=0.02). UFS-QOL symptoms and number of fibroids were not associated (p= 0.09). No statistically significant difference for PBAC score was found between patients with 1 or 2 fibroids (p=0.94).

DISCUSSION

Main findings

The results of the present study generally support our hypothesis that stronger fibroid vascularisation is related to more symptoms over time (12 months follow up). Both fibroid vascularisation and fibroid volume are associated with an increase of the amount of menstrual blood loss and fibroid related symptoms over time. Subgroup analyses for type of fibroid (submucous, intramural and subserosal) showed a statistically significant association between baseline VI and PBAC score at 12 months follow up for intramural fibroids. For baseline fibroid volume an association was found for bleeding and fibroid related symptoms in the group with intramural fibroids. Women with 2 fibroids at baseline noted on average a 10 point higher UFS-QOL quality of life score over time than women with 1 fibroid at baseline.

Strengths and limitations

This is the first study comparing vascularisation and fibroid related symptoms in a longitudinal setting with repeated measurements. We used validated tools to measure our outcomes. One experienced examiner performed all ultrasound and offline measurements, excluding the risk of intra-observer variation concerning the ultrasound findings. Applied techniques to measure 3D volume and vascularity were tested in a previous study that determined the optimal settings in fibroid measurement [9]. To exclude possible influence from therapy on fibroid vascularisation, only women without hormonal or surgical therapy were included. We adjusted for several possible confounders and performed subgroup analyses. However this selection has some negative aspects. It resulted in small sample sizes, hampering the power of our study. One of the reasons that subgroup analyses and analyses at a single time point were not significant might be due to this problem. By excluding women that received surgical therapy, we selected a group of women with relatively mild symptoms. This group is of interest because one would want to be able to predict the occurrence of symptoms in order to start treatment or refrain from treatment. Excluding patients that chose therapy (thus with more complaints) could explain that in our study we did not find a statistically significant association between vascularity at baseline and an increase in PBAC score over time when adjusted for confounders. Women with more symptoms and submucous fibroids most probably chose some sort of treatment. Another explanation may be that submucous fibroids, irrespective of vascularisation, already cause more complaints (due to their location) and vascularisation is less of influence in this type of fibroid. The relatively limited number of women in this group could have played a role as well. Given our selection, the results cannot be extrapolated to women receiving therapy or women with an extensive number of fibroids. Unfortunately not all women completed the questionnaires correctly despite clear instructions. A more complete follow-up could have provided stronger conclusions between fibroid vascularisation and symptoms. There is room for improvement; for instance using electronic questionnaires and using the patients' own smartphone will facilitate completion and could provide clearer instructions and leave less room for error. Questionnaires should be as easily accessible as possible for patients.

Interpretations

Many theories are reported as to why fibroids cause heavy menstrual bleeding. It is hypothesised that an enlarged endometrial surface area with fragile vessels causes bleeding problems [25;26]. Another theory suggests that a reduced myometrial contractility, due to the presence of fibroids, causes bleeding problems. Several observational studies demonstrate a causative relationship between fibroids and abnormal uterine bleeding.

Women with abnormal bleeding were found to have a higher prevalence of fibroids than asymptomatic women and conversely women with fibroids were found to have an increased risk of heavy menstrual bleeding and other symptoms like dyspareunia and non-cyclic pelvic pain compared to women without fibroids [2;27-29].The clinical consensus among gynaecologists is that submucous fibroids are associated with heavy menstrual bleeding. We expected to find this association but instead we found an association between intramural fibroids and PBAC score. But as discussed previously this is mainly explained by our selection criteria, excluding symptomatic women requiring therapy. The relation between fibroid volume and symptoms is supported by previous studies that reported fibroid size was the main factor to be associated with bleeding symptoms. Risk of heavy menstrual bleeding, without other fibroid specific symptoms, increased with size of fibroids (but were not associated with type of fibroid) [2].

Previous studies that assessed fibroid vascularity and symptoms used different methods to assess vascularity, like flow velocity or the presence of a leiomyoma artery, sometimes taking leiomyoma volume or uterine weight into account [13-15]. These studies report about gene expression, increased flow in the uterine artery and report that vascularity of leiomyoma can be useful as a predictor of leiomyoma growth. They report little about the relation of vascularity and symptoms. These studies also used different methods to assess symptoms, from not validated questionnaires [13;15] to the alkaline hematin method to assess heavy menstrual bleeding [14]. Only one study had follow-up moments every three months during a year [15]. We used vascular index (VI) to assess fibroid vascularity. We found an association between vascularity and amount of menstrual blood loss over time, especially in intramural fibroids. Furthermore, we used validated questionnaires to assess amount of bleeding and symptoms every three months during one year. In this study, health related quality of life scores were not significantly affected, possibly because this is a less responsive outcome since it also measures factors that are influenced by general quality of life and eventual life events, overcoming the subtle changes in symptoms during one year. PBAC questionnaires were often poorly filled out by patients. An explanation may be that in this study patients were asked to keep track of their blood loss on paper instead of web based.

CONCLUSIONS

This study showed that both fibroid vascularisation and fibroid volume are associated with an increase of the amount of menstrual blood loss and fibroid related symptoms over time. These results are promising and encourage future studies to confirm that assessing fibroid volume and vascularisation using 3D PD ultrasound could potentially

be used in the future for predicting symptoms and opting for treatment or expectative management. 3D PD can easily be performed in clinical practice but should not be implemented before future studies (in a more heterogeneous group of patients with fibroids) confirm its validity. More research is needed to help understand and predict fibroid growth and fibroid related symptoms in larger studies enabling correction for all possible relevant predictive factors including fibroid classification, race, smoking and body mass index (BMI) etcetera.

Acknowledgements

None.

Disclosure of Interests

Dr. Huirne reports grants from NWO, ZonMW, Olympus, Preglem, Celenova and Samsung. All grants are received outside the submitted work. Dr. Brölmann reports an advisory function for Olympus Europe with reimbursement. The other authors have nothing to disclose.

Contribution to Authorship

IK: contributions to design, acquisition of data analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. LN: substantial contributions to conception and design, acquisition of data analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. WH: substantial contributions to conception and design, drafting the article or revising it critically for important intellectual content. JT: analysis and interpretation of data, drafting the article or revising it critically for important intellectual content. HB: substantial contributions to conception and design, drafting the article or revising it critically for important intellectual content. JH: substantial contributions to conception and design, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content.

Details of Ethics Approval

Study was approved by the VUmc Medical Ethical Committee at 8-3-2012, number 2012/092.

Funding

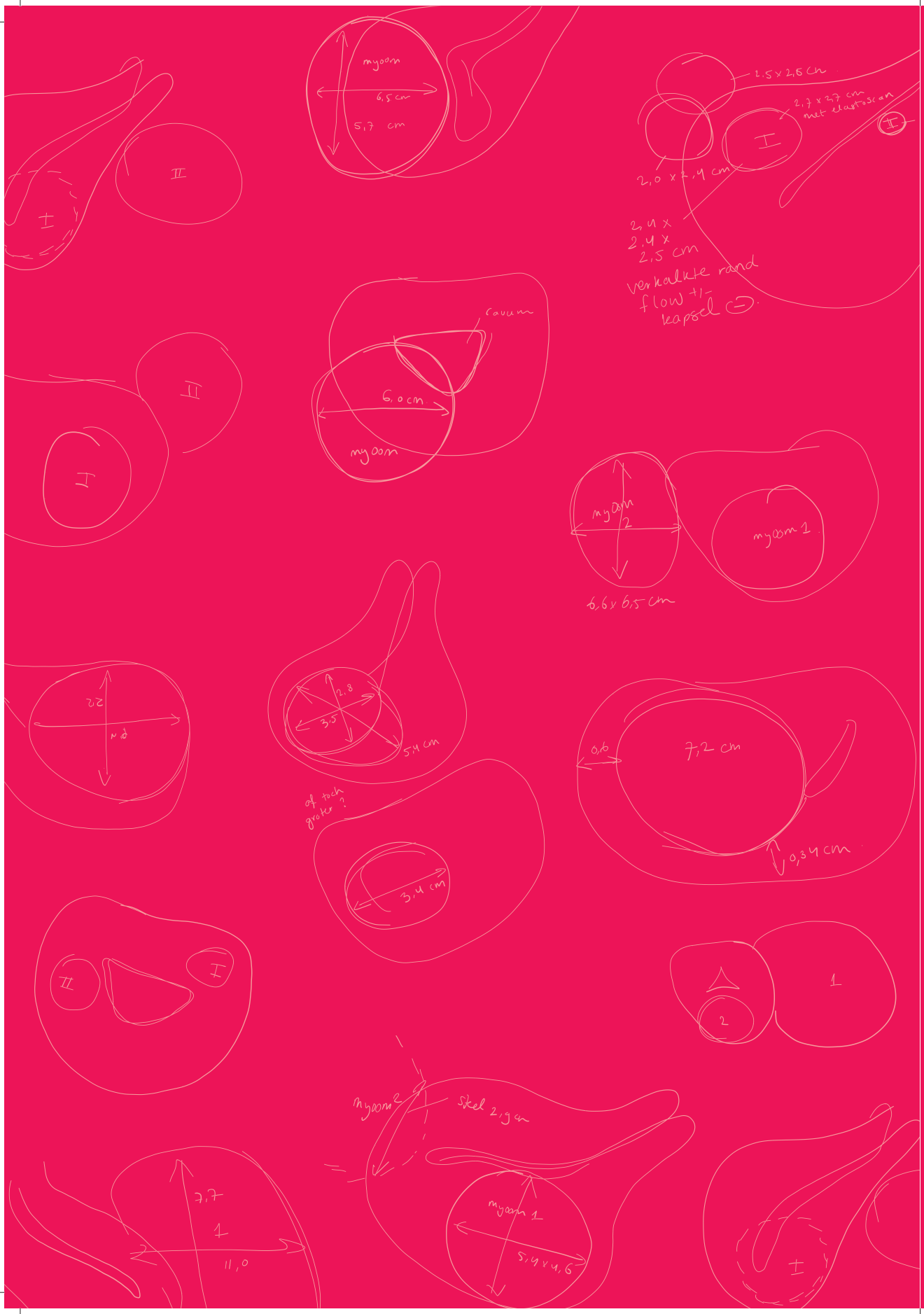
None.

REFERENCES

1. Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril 2007 Apr;87(4):725-36.
2. Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol 2003 Mar;101(3):431-7.
3. Gupta S, Jose J, Manyonda I. Clinical presentation of fibroids. Best Pract Res Clin Obstet Gynaecol 2008 Aug;22(4):615-26.
4. Stovall DW. Clinical symptomatology of uterine leiomyomas. Clin Obstet Gynecol 2001 Jun;44(2):364-71.
5. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009 Apr;91(4):1215-23.
6. Klatsky PC, Tran ND, Caughey AB, Fujimoto VY. Fibroids and reproductive outcomes: a systematic literature review from conception to delivery. Am J Obstet Gynecol 2008 Apr;198(4):357-66.
7. Golan A, Sagiv R, Berar M, Ginath S, Glezerman M. Bipolar electrical energy in physiologic solution--a revolution in operative hysteroscopy. J Am Assoc Gynecol Laparosc 2001 May;8(2):252-8.
8. Munro MG, Critchley HO, Fraser IS. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertil Steril 2011 Jun;95(7):2204-8, 2208.
9. Nieuwenhuis LL, Keizer AL, Stoelinga B, Twisk J, Hehenkamp W, Brolmann H, et al. Fibroid vascularisation assessed with three-dimensional power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective cohort study. BJOG 2017 Feb 17.
10. Nieuwenhuis LL, Betjes HE, Hehenkamp WJ, Heymans MW, Brolmann HA, Huirne JA. The use of 3D power Doppler ultrasound in the quantification of blood vessels in uterine fibroids: feasibility and reproducibility. J Clin Ultrasound 2015 Mar;43(3):171-8.
11. Minsart AF, Ntoutoume SF, Vandenhoute K, Jani J, Van PC. Does three-dimensional power Doppler ultrasound predict histopathological findings of uterine fibroids? A preliminary study. Ultrasound Obstet Gynecol 2012 Dec;40(6):714-20.
12. Degani S, Tamir A, Leibovitz Z, Shapiro I, Gonen R, Ohel G. Three-dimensional power Doppler in the evaluation of painful leiomyomas and focal uterine thickening in pregnancy. Int J Gynaecol Obstet 2007 Nov;99(2):122-6.
13. Tsiligiannis SE, Zaitseva M, Coombs PR, Shekleton P, Olshansky M, Hickey M, et al. Fibroid-associated heavy menstrual bleeding: correlation between clinical features, Doppler ultrasound assessment of vasculature, and tissue gene expression profiles. Reprod Sci 2013 Apr;20(4):361-70.
14. Farmakides G, Stefanidis K, Paschopoulos M, Mamopoulos M, Lolis D. Uterine artery Doppler velocimetry with leiomyomas. Arch Gynecol Obstet 1998;262(1-2):53-7.

15. Tsuda H, Kawabata M, Nakamoto O, Yamamoto K. Clinical predictors in the natural history of uterine leiomyoma: preliminary study. J Ultrasound Med 1998 Jan;17(1):17-20.
16. Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS, Perkins A, et al. Evaluation of the effect of machine settings on quantitative three-dimensional power Doppler angiography: an in-vitro flow phantom experiment. Ultrasound Obstet Gynecol 2008 Sep;32(4):551-9.
17. Collins SL, Stevenson GN, Noble JA, Impey L, Welsh AW. Influence of power Doppler gain setting on Virtual Organ Computer-aided AnaLysis indices in vivo: can use of the individual sub-noise gain level optimize information? Ultrasound Obstet Gynecol 2012 Jul;40(1):75-80.
18. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990 Aug;97(8):734-9.
19. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. BJOG 2000 Mar;107(3):320-2.
20. Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. Obstet Gynecol 1995 Jun;85(6):977-82.
21. Janssen CA. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. Eur J Obstet Gynecol Reprod Biol 1996 Dec;70(1):21-2.
22. Zakherah MS, Sayed GH, El-Nashar SA, Shaaban MM. Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: diagnostic accuracy compared to alkaline hematin. Gynecol Obstet Invest 2011;71(4):281-4.
23. Hald K, Lieng M. Assessment of periodic blood loss: interindividual and intraindividual variations of pictorial blood loss assessment chart registrations. J Minim Invasive Gynecol 2014 Jul;21(4):662-8.
24. Spies JB, Coyne K, Guaou GN, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol 2002 Feb;99(2):290-300.
25. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Hum Reprod Update 1996 Jul;2(4):295-306.
26. Patterson-Keels LM, Selvaggi SM, Haefner HK, Randolph JF, Jr. Morphologic assessment of endometrium overlying submucosal leiomyomas. J Reprod Med 1994 Aug;39(8):579-84.
27. Lippman SA, Warner M, Samuels S, Olive D, Vercellini P, Eskenazi B. Uterine fibroids and gynecologic pain symptoms in a population-based study. Fertil Steril 2003 Dec;80(6):1488-94.
28. Marino JL, Eskenazi B, Warner M, Samuels S, Vercellini P, Gavoni N, et al. Uterine leiomyoma and menstrual cycle characteristics in a population-based cohort study. Hum Reprod 2004 Oct;19(10):2350-5.

29. Clevenger-Hoeft M, Syrop CH, Stovall DW, Van Voorhis BJ. Sonohysterography in premenopausal women with and without abnormal bleeding. Obstet Gynecol 1999 Oct;94(4):516-20.


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

10

General discussion

Imaging of the uterus

In gynaecology, (transvaginal) ultrasound is the most widely used modality to visualize the uterus. Abnormalities can be visualized and classified using ultrasound. Correct diagnosis is crucial for treatment options and success. With three dimensional (3D) ultrasound a volume of the uterus can be stored and analysed directly on the machine or at a personal computer whenever needed. The advantage of 3D ultrasound above 2D ultrasound is that it allows examination of the uterus from any angle and in any plane. It also allows the quantitative measurement of the vascularity of the uterus and its abnormalities. The latter may facilitate differentiation between various myometrial and endometrial pathologies and in theory may predict future behaviour or their responsiveness to therapy.

Imaging of the cavity

In this thesis we tried to apply a systematic approach in answering various research questions. Firstly, 3D gel installation sonography (3D GIS) was validated for its use to assess intra-uterine disorders and afterwards tested in clinical practice (chapter 2 and 3). Besides the accuracy we also studied whether results would improve treatment (planning of hysteroscopic procedure). Secondly the literature was reviewed to provide an overview of reported 3D saline infusion sonography (3D SIS) accuracy compared to 2D SIS. A limitation for both chapter 2 and 3 is that we included patients with a suspected intracavitary abnormality on conventional ultrasound, resulting in a limited number of patients without an intracavitary abnormality (though common in clinical practice). 3D ultrasonography has the theoretical advantage of a more accurate measurement of the fibroid protrusion in the uterine cavity because perceived protrusion depends on the plane where it is measured and in 3D the most proper plane can be visualized in contrast with 2D ultrasound. Our results showed moderate agreement for the proportion of fibroid protrusion into the uterine cavity (FIGO-classification of fibroids), which was less than reported by others [1]. An explanation may lie in the level of experience of the sonographers and quality of used volumes, since 3D volumes were taken during routine clinical practice and not only by a selected group of experienced sonographers like in most other studies. The purpose was to evaluate accuracy in clinical practice. It has been reported that agreement between less experienced performers and experienced performers shows significantly different results [2]. Fortunately the learning curve is steep. Since hysteroscopy is the golden standard to detect presence of an intracavitary abnormality, it was used as a reference test. However hysteroscopy might be less suitable to assess percentage of fibroid protrusion into the uterine cavity as one only sees the surface of the uterine cavity. It can provide information to classify submucous fibroids but the level of fibroid protrusion might be influenced by the applied intra-

uterine pressure. In addition, hysteroscopy can underestimate protrusion (lack of vision) but can also overestimate when procedure is difficult to perform. Variation in the classification of the difficulty of the procedure between observers could have been prevented by blinded and objective evaluation by one independent observer using video recordings of the procedure. Secondly it is difficult in such a setting for 3D GIS to increase sensitivity, as 2D GIS is already quite accurate.

Findings implicate that 3D SIS can be used where the technology and appropriate expertise are available. 2D SIS and 3D SIS can both be considered an alternative for hysteroscopy when intracavitary pathology is suspected in both sub fertile women and women with abnormal uterine bleeding. The use of 3D ultrasound without contrast in classifying fibroids might be of benefit to the patient, because the introduction of fluid or gel is no longer necessary and therefore less of a burden. Although this technique seems to be feasible, it still needs improvement before its value in the diagnostic pathway can be determined in future studies (chapter 5). 3D SIS is also not ready to replace 2D SIS in clinical practice since it is unsure whether it will improve (planning of) treatment. It is unknown how effective 3D SIS is when 2D SIS is inconclusive and if purchasing materials (3D probe, software, etc.) and learning curve outweigh the limited benefit. These benefits and costs must be evaluated in future studies. When found accurate and effective, implementation and training is recommended. Training is essential since the experience of the performing sonographer or physician affects accuracy and outcome of ultrasound effects (choice of) treatment. Current treatment for intracavitary abnormalities is still performed with hysteroscopic approach but with upcoming other minimal invasive therapies as ultrasonically guided ablation this information is becoming increasingly crucial. In that case the slightly more accurate 3D SIS may be of great value, improvement can specially be expected for submucous and intramural fibroids since treatment choice and planning are based on SIS findings.

Measuring fibroids vascularisation

To measure vascularisation in a volume of interest (in our case a fibroid) one can use Magnetic resonance imaging (MRI), or several (Doppler) ultrasound techniques [3-6]. MRI showed better reproducibility than ultrasound [7,8] but ultrasound has improved over the years resulting in a clearer image. MRI on the other hand is less available, more expensive and more time consuming for the patient. In our studies we focused on measuring vascularisation with Doppler ultrasound, we did not compare vascularisation between ultrasound and MRI. We first validated 3D power Doppler (3D PD) ultrasonography and found an almost perfect interobserver agreement for various vascular parameters in fibroids. The vascular index (VI) was found to be the most reproducible Power Doppler

parameter (over the flow index and vascular flow index). In particular the manually acquired VI of the fibroid and the fibroid's capsule had the best agreement. Our results furthermore indicated that a predetermined most optimal fixed gain setting was not different from an individually most optimal chosen gain in vascular assessment of fibroids using 3D PD. We found no influence of the cardiac cycle on the vascularity of the fibroids. Although some questions remain to be answered, we do not think the cardiac cycle is of major influence. The same accounts for the menstrual cycle. On theoretical grounds there might be changes in vascularity throughout the menstrual cycle. It is reported that vascularity of endometrium is high in the secretory phase [9]. It is unknown whether the vascularization of the myometrium changes during the menstrual cycle. We do know that it is of influence on the myometrial contractility [10, 11]. Women with pain during menstruation showed higher vascularisation of the myometrium [12]. It is possible that the different conditions during the menstrual cycle are of influence on vascularity of the myometrium, endometrium and fibroids. Future studies need to focus on this. Vascularisation at different moments in the cycle can be studied or measurements should preferably be performed in the same phase or at the same day in each following cycle.

Fibroids vascularisation and predicting behaviour and symptoms

In our clinical study, women with fibroids were followed using 3D PD ultrasound over a period of 12 months. Baseline vascularisation (VI) of the fibroid measured with 3D Power Doppler was found to be correlated with changes in fibroid volume at 12 months. This study underlines our hypothesis that highly vascularised fibroids tend to grow faster than poorly vascularised fibroids. Findings implicate that in women with uterine fibroids without therapy, 3D Power Doppler may be used to predict fibroid growth. If this finding is confirmed in other studies, we might be able to predict fibroid growth in an individual patient and will be able to advice on follow-up interval and treatment, also in case of asymptomatic patients. This way we can select patients that are prone to rapidly growing fibroids that have a higher chance of becoming symptomatic. If we monitor those patients closely, we might avoid major surgery and on the other hand might prevent surgery in patients with a vascular pattern that predicts moderate to absent growth and development of symptoms. Our findings only point into this direction and raise new questions that need to be answered, but it is a new and exciting finding that requires confirmation studies and refinement of the technique. Another question that needs to be answered is whether a follow up period of 12 months is long enough to be able to predict fibroid growth. Other studies reported a large variation in changes in fibroid growth; different fibroids in one woman may grow at different rates and up to one fifth of fibroids regress spontaneously in premenopausal women [13-15]. The increase

in volume we found could in theory also be a results of temporary necrosis or congestion and associated fluid accumulation that is expected to result in a decreases volume at a longer follow-up. A longer follow up may answer this question. We additionally hypothesized that fibroid vascularisation is associated with heavy menstrual bleeding and fibroid related quality of life in women with one or more submucosal or intramural fibroids and that it is associated with a stronger increase of symptoms over time. We found vascularisation and size to be related to an increase in symptoms after 12 months follow-up. This is in line with other studies that reported that the risk of heavy menstrual bleeding, increased with size of fibroids but were not associated with type of fibroid [16-19]. Thus, vascularisation (VI) might be of additional help in the future to predict which fibroids will potentially cause growth and increase of symptoms over time and may support women and their gynaecologists in therapeutic decision making. Future studies need to be performed to confirm these findings.

Future perspectives

Although 3D power Doppler is a promising technique, it is also one in development. It has several uncertainties and challenges. Attenuation can be a problem for power Doppler in fibroids as the signal might not be sensitive enough in larger fibroids (object far from the ultrasound probe). Also for normal (trans vaginal) ultrasound, fibroids larger than 8 cm are difficult to delineate and do not seem to fit in the scan sector. Our results are promising and a first step in integrating vascularity as standard diagnostic test. However, results need to be confirmed with longer follow up to observe a larger or more precise effect. Other techniques could be considered and investigated to minimise the effect of machine settings. Maybe a subjective impression of the vascularity, as proposed by Exacoustos et al is equivalent to the vascular index [20]. Another challenge that needs to be resolved is that absolute values of vascular parameters are dependent on the ultrasound machine (settings) used. We were able to follow patients over time but absolute values or cut-off values are not yet available. An international consensus on how to use this technique is lacking. We need to study further how and when vascularity can best be objectified, uncertainties need to be addressed before it can be implemented in clinical practice and results between different studies can be compared. Due to the lack of cut-off values we cannot inform women about the growth potential of their fibroids by a single measurement. It would also be interesting to compare vascular indices from patients with mild symptoms versus patients with severe symptoms (corrected for fibroid size). Additionally we need larger studies to allow correction for all possible confounders in order to develop models in the prediction of natural course of fibroids or responsiveness to therapy under different circumstances. Patients are choosing minimal invasive options more frequently and not only because of a future pregnancy

wish. In studies with MRI we learned that vascularity of the fibroid can predict outcome of minimal invasive treatment (success of embolization was greater for well vascularised fibroids) and can therefore also help choosing the type of treatment [21-23]. 3D PD before and after minimal invasive treatment has not been studied yet.

Differentiating between abnormalities

Over the past few years uniform terminology in uterine disorders and criteria for their appearances on ultrasound are reported [6, 24, 25]. These ultrasound criteria will not only have a huge impact on the use of ultrasound, they probably also improve (consensus about) diagnosis and therefore treatment and it enables comparison between studies. Conventional techniques like SIS, (power) Doppler and elastography [26-28] can improve the diagnostic value of ultrasound in differentiating between abnormalities. Ultrasound criteria can be extended for the several additional ultrasound techniques and measurements should be uniform [29]. When we agree how, when and with which technique we are measuring and report the same parameters, researchers can compare their work and collaborate in international studies. This is especially important in rare diseases like uterine leiomyosarcomas. Collecting data from larger populations where ultrasound is performed systematically we might be able to answers some urgent questions. Since incidence of leiomyosarcomas is low, we are still struggling to find the optimal differentiation between these malignant tumours and the common benign fibroids. Differentiation is especially important when conservative treatment is considered. In this case often a pathological examination will lack and diagnosis can only be made by imaging techniques. Power Doppler has not yet been studied in the distinction between those tumours but it is reported that cellularity in the fibroid corresponds with the vascular indices measured with power Doppler [30]. Vasularity is studied more widely using Color doppler and has been reported to be of assistence in identifying and differentiating between benign and malignant uterine tumors [6, 20, 31-35]. Quantifying vascularity is a first step. Subsequently the diagnostic accuracy (sensitivity and specificity) of this technique in detecting malignant tumours must be studied to ultimately provide a cut-off value. A cut-off value would be a huge step but given the limited prevalence of leiomyosarcomas this will not be easy.

Ultrasound beyond

Even with our limited understanding of fibroids, new minimal invasive options are being developed quickly. Hopefully a greater understanding may lead to more specific/targeted innovative treatments where local treatments might replace systemic (hormonal) therapy or radical surgery. In the best case scenario we might even be able to prevent polyps and fibroids from originating. Besides the female hormones oestrogen

and progesterone, growth factors and factors providing angiogenesis play an important role in fibroid growth [36]. Medication that suppresses several growth factors is reported to reduce fibroid volume. In the field of oncology, ultrasound-based therapy and tumor targeting drug delivery is studied increasingly. Ultrasound diagnosis can be improved by the use of gas-filled microbubbles as ultrasound contrast agents [37]. Also in others fields like cardiology (loaded) microbubbles [38] are used for therapy reasons. If these new techniques are successful, we can deliver therapy exactly where it is needed. Ultrasound (three dimensional, doppler, contrast, etc) can facilitate in visualising the uterus and the target condition before, during and after treatment.

Practice and education

Another imported part in optimising 3D ultrasound performance is the software used. It can be improved by making it easier to work with and faster in use. Secondly, 3D ultrasound volumes could be integrated in patient electronical hospital records similar to other radiological exams. This would facilitate the diagnostic process. Another technique to minimise interobserver variation or missing diagnosis is the use of computers analysing the ultrasound volumes. Computer-aided diagnosis in ultrasound is investigated in breast, thyroid, fetal hart and other organs and show promising results [39-42]. Besides the ease of offline analysis of 3D images, this technique in which computers can help us detect and differentiate between abnormalities is an extra function that may be useful in gynaecological disorders too.

Education is important for future colleagues and the results of their scientific research. Ultrasonography is an important part of daily activities of a gynaecologist. It is therefore logical and necessary to include ultrasound training in the residency program. Similar to foetal ultrasound evaluation, ultrasound of the female pelvic organs should be standardized both in technique as in reporting. Training is essential since the experience of the performing ultra-sonographer influences diagnostic accuracy and subsequently treatment. Ultrasound is well established to be very accurate in diagnosing all sorts of gynaecological abnormalities in experienced hands. If we want to successfully introduce these diagnostic and minimal invasive techniques in gynaecology practice in the future, we must be frontrunners in education and training of ultrasound techniques.

Conclusion

Ultrasound is indispensable in women's health care and is continuously developing and improving. Findings in this thesis confirm that 3D (Power Doppler) ultrasound has great potential in the diagnosis and differentiation of benign uterine disorders and encourage future studies on these topics for its use in gynaecology.

REFERENCES

1. Lee C, Salim R, Ofili-Yebovi D, Yazbek J, Davies A, Jurkovic D. Reproducibility of the measurement of submucous fibroid protrusion into the uterine cavity using three-dimensional saline contrast sonohysterography. Ultrasound Obstet Gynecol. 2006 11/2006;28(6):837-41.
2. Beemsterboer SN, Thurkow AL, Verstraeten R, Brolmann HA. Reproducibility of saline contrast sonohysterography for the detection of intracavitary abnormalities in women with abnormal uterine bleeding. Ultrasound Obstet Gynecol. 2008 4/2008;31(4):445-9.
3. Miyague AH, Raine-Fenning NJ, Pavan TZ, Polanski LT, Baumgarten MN, Nastri CO, et al. Influence of gain adjustment on 3-dimensional power Doppler indices and on spatiotemporal image correlation volumetric pulsatility indices using a flow phantom. J Ultrasound Med. 2013 10/2013;32(10):1831-6.
4. Soares CA, Miyague AH, Filho FM, Raine-Fenning N, Martins WP. Fractional moving blood volume (FMBV) concept can be applied to 3D power Doppler quantification. Ultrasound Obstet Gynecol. 2013 1/2013;41(1):98-9.
5. Stevenson GN, Collins SL, Welsh AW, Impey LW, Noble JA. A technique for the estimation of fractional moving blood volume by using three-dimensional power Doppler US. Radiology. 2015 1/2015;274(1):230-7.
6. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015 Sep;46(3):284-98.
7. Dueholm M, Lundorf E, Sorensen JS, Ledertoug S, Olesen F, Laursen H. Reproducibility of evaluation of the uterus by transvaginal sonography, hysterosonographic examination, hysteroscopy and magnetic resonance imaging. Hum Reprod. 2002 1/2002;17(1):195-200.
8. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol. 2002 3/2002;186(3):409-15.
9. Sharma K, Bora MK, Venkatesh BP, Barman P, Roy SK, Jayagurunathan U, et al. Role of 3D Ultrasound and Doppler in Differentiating Clinically Suspected Cases of Leiomyoma and Adenomyosis of Uterus. J Clin Diagn Res. 2015 Apr;9(4):QC08-12.
10. Akerlund A. Vascularization of human endometrium. Uterine blood flow in healthy condition and in primary dysmenorrhea. Ann N Y Acad Sci. 1994 1994;734:47.
11. Hauksson A, Akerlund M, Melin P. Uterine blood flow and myometrial activity at menstruation, and the action of vasopressin and a synthetic antagonist. Br J Obstet Gynaecol. 1988 Sep;95(9):898-904.
12. Royo P, Alcazar JL. Three-dimensional power Doppler assessment of uterine vascularization in women with primary dysmenorrhea. J Ultrasound Med. 2008 7/2008;27(7):1003-10.

13. DeWaay DJ, Syrop CH, Nygaard IE, Davis WA, Van Voorhis BJ. Natural history of uterine polyps and leiomyomata. Obstet Gynecol. 2002 2002;100(1):3-7.

14. Mavrelos D, Ben-Nagi J, Holland T, Hoo W, Naftalin J, Jurkovic D. The natural history of fibroids. Ultrasound Obstet Gynecol. 2010 Feb;35(2):238-42.

15. Peddada SD, Laughlin SK, Miner K, Guyon JP, Haneke K, Vahdat HL, et al. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci U S A. 2008 12/16/2008;105(50):19887-92.

16. Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003 2003;101(3):431-7.

17. Clevenger-Hoeft M, Syrop CH, Stovall DW, Van Voorhis BJ. Sonohysterography in premenopausal women with and without abnormal bleeding. Obstet Gynecol. 1999 1999;94(4):516-20.

18. Marino JL, Eskenazi B, Warner M, Samuels S, Vercellini P, Gavoni N, et al. Uterine leiomyoma and menstrual cycle characteristics in a population-based cohort study. Hum Reprod. 2004 Oct;19(10):2350-5.

19. Lippman SA, Warner M, Samuels S, Olive D, Vercellini P, Eskenazi B. Uterine fibroids and gynecologic pain symptoms in a population-based study. Fertil Steril. 2003 Dec;80(6):1488-94.

20. Exacoustos C, Romanini ME, Amadio A, Amoroso C, Szabolcs B, Zupi E, et al. Can gray-scale and color Doppler sonography differentiate between uterine leiomyosarcoma and leiomyoma? J Clin Ultrasound. 2007 Oct;35(8):449-57.

21. Isonishi S, Coleman RL, Hirama M. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. AJOG. 2008 2008;198(3):270-e1.

22. Funaki F, Fukunishi H, Funaki T, Sawada K, Kaji Y, Maruo T. Magnetic resonance-guided focused ultrasound surgery for uterine fibroids: relationship between the therapeutic effects and signal intensity of preexisting T2-weighted magnetic resonance images. AJOG. 2007 2007;196(2):e1-e6.

23. Yoon SW, Lee C, Kim KA, Kim SH. Contrast-Enhanced Dynamic MR Imaging of Uterine Fibroids as a Potential Predictor of Patient Eligibility for MR Guided Focused Ultrasound (MRgFUS) Treatment for Symptomatic Uterine Fibroids. Obstet Gynecol Int. 2010 2010;2010.

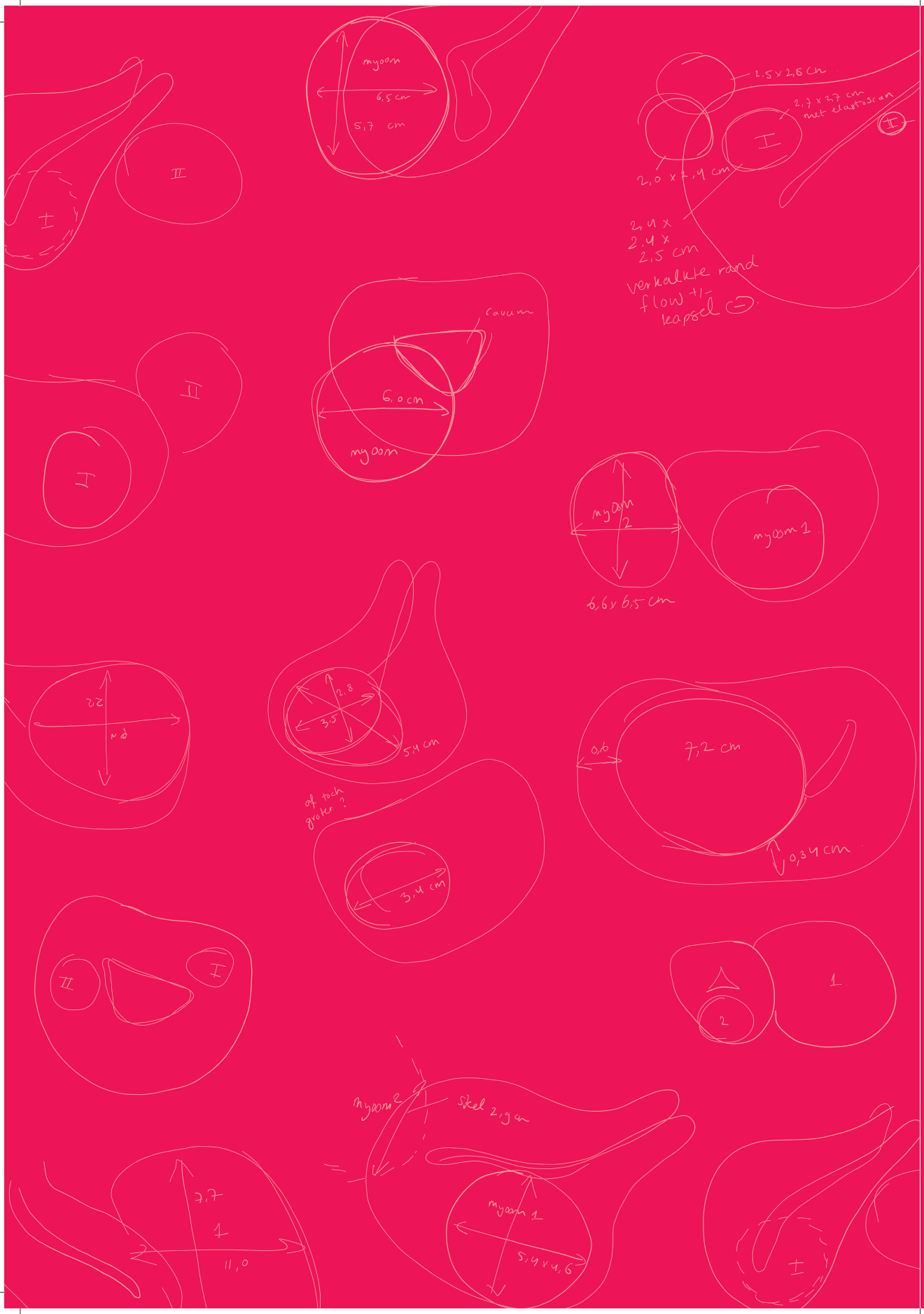
24. Munro MG, Critchley HO, Broder MS, Fraser IS. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011 Apr;113(1):3-13.

25. Dueholm M, Hjorth IM. Structured imaging technique in the gynecologic office for the diagnosis of abnormal uterine bleeding. Best Pract Res Clin Obstet Gynaecol. 2017 Apr;40:23-43.

26. Stoelinga B, Hehenkamp WJ, Brolmann HA, Huirne JA. Real-time elastography for assessment of uterine disorders. Ultrasound Obstet Gynecol. 2014 Feb;43(2):218-26.

27. Czuczwar P, Wozniak S, Szkodziak P, Kudla MJ, Pyra K, Paszkowski T. Elastography Improves the Diagnostic Accuracy of Sonography in Differentiating Endometrial Polyps and Submucosal Fibroids. J Ultrasound Med. 2016 Nov;35(11):2389-95.
28. Swiatkowska-Freund M, Preis K. Cervical elastography during pregnancy: clinical perspectives. Int J Womens Health. 2017;9:245-54.
29. Khan K. The CROWN Initiative: journal editors invite researchers to develop core outcomes in women's health. BJOG. 2016 Sep;123 Suppl 3:103-4.
30. Minsart AF, Ntoutoume SF, VAndenhoute K, Jani J, Van PC. Does three-dimensional power Doppler ultrasound predict histopathological findings of uterine fibroids? A preliminary study. Ultrasound Obstet Gynecol. 2012 12/2012;40(6):714-20.
31. Jayakrishnan K, Koshy AK, Manjula P, Nair AM, Ramachandran A, Kattoor J. Endometrial stromal sarcoma mimicking a myoma. Fertil Steril. 2009 Nov;92(5):1744-6.
32. Aviram R, Ochshorn Y, Markovitch O, Fishman A, Cohen I, Altaras MM, et al. Uterine sarcomas versus leiomyomas: gray-scale and Doppler sonographic findings. J Clin Ultrasound. 2005 Jan;33(1):10-3.
33. Szabo I, Szantho A, Csabay L, Csapo Z, Szirmai K, Papp Z. Color Doppler ultrasonography in the differentiation of uterine sarcomas from uterine leiomyomas. Eur J Gynaecol Oncol. 2002;23(1):29-34.
34. Hata K, Hata T, Maruyama R, Hirai M. Uterine sarcoma: can it be differentiated from uterine leiomyoma with Doppler ultrasonography? A preliminary report. Ultrasound Obstet Gynecol. 1997 Feb;9(2):101-4.
35. Bonneau C, Thomassin-Naggara I, Dechoux S, Cortez A, Darai E, Rouzier R. Value of ultrasonography and magnetic resonance imaging for the characterization of uterine mesenchymal tumors. Acta Obstet Gynecol Scand. 2014 Mar;93(3):261-8.
36. Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update. 2014 Mar-Apr;20(2):194-216.
37. Guvener N, Appold L, de Lorenzi F, Golombek SK, Rizzo LY, Lammers T, et al. Recent advances in ultrasound-based diagnosis and therapy with micro- and nanometer-sized formulations. Methods. 2017 May 24.
38. Woudstra L, Krijnen PA, Bogaards SJ, Meinster E, Emmens RW, Kokhuis TJ, et al. Development of a new therapeutic technique to direct stem cells to the infarcted heart using targeted microbubbles: StemBells. Stem Cell Res. 2016 Jul;17(1):6-15.
39. Chabi ML, Borget I, Ardiles R, Aboud G, Boussouar S, Vilar V, et al. Evaluation of the accuracy of a computer-aided diagnosis (CAD) system in breast ultrasound according to the radiologist's experience. Acad Radiol. 2012 Mar;19(3):311-9.
40. Yu Q, Jiang T, Zhou A, Zhang L, Zhang C, Xu P. Computer-aided diagnosis of malignant or benign thyroid nodes based on ultrasound images. Eur Arch Otorhinolaryngol. 2017 Apr 07.

41. Abuhamad A, Falkensammer P, Reichartseder F, Zhao Y. Automated retrieval of standard diagnostic fetal cardiac ultrasound planes in the second trimester of pregnancy: a prospective evaluation of software. Ultrasound Obstet Gynecol. 2008 Jan;31(1):30-6.
42. Uittenbogaard LB, Haak MC, van Vugt JM. Feasibility of automated 3-dimensional fetal cardiac screening in routine ultrasound practice. J Ultrasound Med. 2009 Jul;28(7):881-8.


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
myoom 2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
2
1
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6

11

Summary in English and Dutch

SUMMARY THESIS

Chapter I gives a general introduction and describes the outline of the thesis. We focused on the most common abnormalities of the uterus; fibroids and intracavitary abnormalities. Intracavitary polyps are focally growing abnormalities within the uterine cavity arising from the endometrium. Leiomyomas or fibroids are benign monoclonal tumours arising from the smooth muscle cells of the myometrium. These benign abnormalities can cause several symptoms including abnormal uterine bleeding and subfertility. More than half of the women will experience these problems during their life. Heavy menstrual bleeding can result in anaemia, interfere with daily activities and have a physical, emotional, sexual and social impact on daily live. Although the majority of fibroids are asymptomatic, up to 25% cause problems. Fibroids can have a negative impact on women's lives, cause a major public health-care burden and are worldwide still the leading cause for hysterectomy.

In gynaecology, (transvaginal) ultrasound is the most widely used modality to visualize the uterus. Abnormalities can be visualized and classified using ultrasound. Ultrasound is usually a two-dimensional image. With three-dimensional (3D) ultrasound a volume of the uterus can be stored and analysed directly on the machine or at a personal computer whenever needed. The advantage of 3D ultrasound above 2D ultrasound is that it allows examination of the uterus from any angle and in any plane. This potentially allows the examiner to more accurately classify abnormalities and measure its size and extent of protrusion into the uterine cavity. Imaging vascularity of the uterus can be of additional help in differentiating between abnormalities inside the uterus. A successful treatment is dependent upon the correct diagnosis. Part I of the dissertation deals with the imaging of intracavitary abnormalities using a 3D (gel/water contrast) ultrasound, and part II deals with the imaging of vascularity of fibroids using 3D power Doppler ultrasound.

In **Chapter II** we studied the interobserver and intraobserver variability of three dimensional gel infusion sonography (3D GIS) in the assessment of intrauterine abnormalities. Forty five 3D volumes were reviewed by two independent examiners and one examiner reviewed these samples twice with an interval of 1 month. Type, size and location of the abnormality were recorded together with image quality. We found an substantial to almost perfect interobserver and intraobserver agreement for 3D GIS in detecting the presence of an intracavitary abnormality. Agreement for both interobserver and intraobserver was lower but still moderate for fibroid classification. Quality of the 3D volumes was assessed as poor in 11 out of 45 cases. Reproducibility

increased when poor quality images were excluded. We concluded that interobserver and intraobserver agreement for 3D GIS in the diagnoses of intrauterine abnormalities was substantial to perfect.

In Chapter III we studied whether 3D GIS can improve diagnoses and preoperative planning (compared to 2D GIS). In a prospective cohort study, we studied whether the addition of 3D GIS to 2D GIS improves accuracy for the detection of polyps and fibroids. We were also interested to know if a higher accuracy would improve optimal planning of hysteroscopic procedures in terms of required equipment and expertise. In 110 women with a suspected intra-uterine abnormality, 2D GIS, 3D GIS and a hysteroscopy were performed. Diagnostic accuracy was calculated for the detection of fibroids and polyps with both histology and hysteroscopy as the reference standard. In comparison to 2D GIS, sensitivity increased by using 3D GIS for the detection of fibroids and polyps, without major interference of the specificity. Despite an improved accuracy after the addition of 3D GIS, the planning for hysteroscopic procedures did not improve substantially. We concluded that in daily practise the addition of 3D SIS improved accuracy slightly but hardly improved the planning of hysteroscopic procedures.

Chapter IV reviews the literature about the accuracy of 3D SIS. Thirteen studies (1053 women) reported the accuracy of 3D SIS for focal uterine abnormalities of which 11 studies (846 women) were suitable for meta-analysis and eight reported accuracy according to the type of focal abnormality. The design of the included studies seemed applicable. The main quality problem with the included studies was insufficient reporting of their methods resulting in unclear risk of bias for several of the quality domains assessed. Therefore the overall quality of the evidence was considered low. The summary estimate for sensitivity and specificity was higher for 3D SIS (96.9 % and 99.5%) than for 2D SIS (90.9% and 96.3%) though this difference was not statistically significant. We concluded that low quality evidence showed 3D SIS to be very accurate in detecting intracavitary abnormalities. Summary sensitivity and specificity are higher for 3D SIS but margins of improvement are limited since 2D SIS is already very accurate. 3D SIS is an alternative to 2D SIS where the technology and appropriate expertise is available. Both 2D SIS and 3D SIS should be considered an alternative to diagnostic hysteroscopy when intracavitary pathology is suspected in both subfertile women and those with abnormal uterine bleeding.

In chapter V we focused on 3D ultrasound without gel or saline instillation. GIS and SIS are very accurate in the diagnosis of submucous fibroids but more invasive than conventional 3D ultrasound. Therefore we investigated the accuracy and reliability of 3D ultrasound in classifying submucous fibroids. A prospective pilot study was performed,

including 14 consecutive patients undergoing hysteroscopic myomectomy or fibroid ablation (Sonata™). All patients underwent routine ultrasonography, prior to the surgical procedure. 2D, 3D, 2D SIS and 3D SIS images were stored and percentages of protrusion were estimated. In this pilot study, 3D ultrasound was not as accurate as 2D SIS or 3D SIS in estimating the percentage of protrusion. 3D was not more accurate than 2D in the total group. A moderate interobserver agreement for 3D and a good interobserver agreement for 3D SIS was found. There was a large variation in image quality of individual patients. In particular during the luteal phase, when the endometrium is thick, visibility of the uterine cavity improved. Based on these findings we concluded that refinement of the technique and timing of 3D ultrasound in the evaluation of fibroids should be performed before evaluation in larger studies and before conclusions can be drawn.

In **Chapter VI** we evaluated the interobserver agreement and discriminating value of three-dimensional Power Doppler ultrasound (3D PDUS) in patients with fibroids. 3D PDUS was performed in 19 patients with fibroids and 3D volumes were evaluated by three independent examiners. The following vascular parameters were studied: Vascular Index (VI), Flow Index (FI) and Vascular Flow Index (VFI) of the fibroid, the vascular capsule and of its highest vascular area. Both manual and automatic contour modes were used to calculate the vascular parameters. We found that in the manual contour mode, the VI of the fibroid and the VI of the vascular capsule had the highest interobserver (almost perfect) agreement. Both parameters seem to have good discriminating values, given the large range of these parameters between different fibroids, independent of their volume. We concluded that VI assessed by 3D PDUS was reproducible in the assessment of fibroid vascularisation with good discriminating abilities.

In Chapter VII we evaluated the influence of the cardiac cycle and different gain settings on 3D PD parameters in the assessment of fibroid vascularisation. In 40 patients, 3D PD US was performed using 3 different gain settings: a fixed predetermined gain (50dB), a higher gain (65dB) and an individualised subjectively most optimal gain. Two consecutive 3D PD sweeps were taken to evaluate the effect of the cardiac cycle. For offline measurements, one reviewer recorded the most favourable method of volume calculation and shell size in every fibroid. Volume calculation using the manual mode was preferred over the automatic mode in the majority of cases. A shell of 0.5 cm was most adequate to calculate vascularisation of the fibroids' capsule. To determine vascularity using 3D PD US in uterine fibroids a predetermined fixed gain can be used. By performing a scan of more than 10 seconds, the potential influence of the cardiac cycle on the VI seems limited.

Chapter VIII describes a prospective cohort study were patients with fibroids were followed over time. The objective was to analyse fibroid vascularisation measured with 3D Power Doppler in relation to absolute fibroid volume change during 12 months follow up and in relation to fibroid growth rate per year. In total 66 premenopausal women diagnosed with a maximum of 2 fibroids with expectative management were consecutively included. 3D ultrasound including Power Doppler was performed at baseline, 3, 6 and 12 months. Volume and vascular parameters were calculated using VOCAL software. Baseline fibroid vascularisation (VI) measured with 3D Power Doppler was correlated with fibroid volume at 12 months ($p = 0.02$). An increase of 1% in VI at baseline was associated with a 7.00 cm^3 larger fibroid volume at 12 months. Furthermore, vascularisation was also associated with fibroid growth rate per year ($p=0.04$). We concluded that in women with uterine fibroids without therapy , baseline vascularisation (VI) measured with 3D Power Doppler is correlated with absolute fibroid volume change at 12 months and with fibroid growth rate per year.

In **Chapter IX** we evaluated fibroid vascularisation in relation to symptoms and health related quality of life using 3D Power Doppler parameters in women with expectative management. A prospective cohort study was performed among 53 premenopausal women diagnosed with a maximum of 2 fibroids. 3D sonography including Power Doppler was performed at baseline, 3, 6 and 12 months follow up. Participants were asked to complete PBAC and UFS-QOL questionnaires at baseline and after 3, 6 and 12 months of follow-up. We found that baseline vascularisation (VI) is associated with bleeding symptoms (PBAC score) over time; a 1% higher VI at baseline leads to an 14.6 point increase in PBAC score ($p=0.04$; 95% CI 0.62 – 28.46). When adjusted for fibroid volume at baseline and type of fibroid association was not significant. Fibroid volume at baseline and heavy menstrual bleeding over time are also associated; a 10 cm^3 larger fibroid volume at baseline is associated with a 5.6 point higher PBAC score over time ($p=0.03$, 95% CI 0.05 – 1.07). Subgroups analyses for type of fibroid (submucous, intramural and subserosal) showed a statistically significant association between baseline VI and PBAC score at 12 months follow up for intramural fibroids (regression coefficient 15.4; $p= 0.004$; 95% CI 6.8-24.0). This study demonstrates an association between fibroid vascularisation and heaviness of menstrual bleeding. Vascularisation is also associated with other fibroid related symptoms and quality of life.

In **Chapter X** we discuss the main results, implications and future perspectives. We demonstrated good reproducibility for 3D GIS in the presence of an intracavitary abnormality. We found 3D SIS to be more accurate than 2D SIS but margins of improvement are limited since 2D SIS is already very accurate. Currently, the clinical relevance seems limited. The use of 3D ultrasound without contrast in classifying fibroids is feasible but

still needs improvement before its value in the diagnostic pathway can be determined in future studies. 3D power Doppler is accurate and feasible. The vascular index (VI) is reproducible in fibroids and is related to volume change over 12 months in women without therapy. Vascularisation may also help us to predict increase of symptoms over time. Future research is required for defining the best method of quantifying vascularity, for estimating treatment effect and possibly also for the differentiation of fibroids and sarcomas.

NEDERLANDSE SAMENVATTING PROEFSCHRIFT

Hoofdstuk I geeft een algemene inleiding en beschrijft de opzet van het proefschrift. We richten ons op de meest voorkomende afwijkingen van de baarmoeder. Een voorbeeld hiervan zijn (intracavitaire) poliepen en myomen, dit zijn goedaardige zwellingen die uitgaan van het slijmvlies respectievelijk van de spierlaag in de baarmoeder. Deze afwijkingen kunnen verschillende symptomen veroorzaken, waaronder abnormaal bloedverlies van de baarmoeder en subfertiliteit. Meer dan de helft van de vrouwen zal tijdens hun leven deze problemen ondervinden. Hevig menstrueel bloedverlies kan bloedarmoede veroorzaken, interfereren met dagelijkse activiteiten en een fysieke, emotionele, seksuele en sociale impact hebben op het dagelijks leven. Hoewel de meeste myomen asymptomatisch zijn, veroorzaken tot 25% problemen. Myomen kunnen een negatief effect hebben op het leven van vrouwen, zorgen voor een belangrijke belasting van de gezondheidszorg en zijn wereldwijd nog steeds de belangrijkste oorzaak voor een hysterectomie.

In de gynaecologie is (transvaginale) echografie de meest gebruikte modaliteit om de baarmoeder te visualiseren. Afwijkingen kunnen worden gevisualiseerd en geclassificeerd door middel van echografie. Afhankelijk van de diagnose variëren de behandelingsopties en daarom is het van essentieel belang om de aanwezige pathologie correct te diagnosticeren en te classificeren. Echografie is meestal een tweedimensionale (2D) afbeelding. Met driedimensionale (3D) echografie kan een volume van de baarmoeder opgeslagen en geanalyseerd worden op het echo apparaat of op een persoonlijke computer, wanneer dat nodig is. Het voordeel van 3D echografie boven 2D echografie is de mogelijkheid om de baarmoeder vanuit elke hoek en in elk vlak te kunnen beoordelen. Hierdoor kan de onderzoeker de afwijkingen nauwkeuriger opmeten en de mate van uitpuiling van een afwijking in de baarmoederholte meten (classificeren). Wanneer de beeldvorming van de baarmoederholte onvoldoende is met normale 2D echografie of aan een intracavitaire afwijking (poliep of myoom) wordt gedacht, kan de afwijking beter in beeld worden gebracht door het toedienen van een zoutoplossing of gel in de holte van de baarmoeder. Verder kan het in beeld brengen van de vascularisatie van de baarmoeder en de afwijkingen helpen bij het differentiëren tussen verschillende soorten afwijkingen. 3D Power Doppler echografie kan bloedvaten in de baarmoeder of in een myoom kwantificeren. Dit proefschrift richt zich met name op de diagnostiek van afwijkingen in de baarmoederholte en myomen middels de drie dimensionale (3D) echo, van belang omdat een (geslaagde) behandeling afhankelijk is van de juiste diagnose. Deel I heeft betrekking op de beeldvorming van afwijkingen

in de baarmoederholte met behulp van 3D water of gel contrast echografie, en deel II behandelt de beeldvorming van myomen en vascularisatie middels 3D power Doppler echografie.

In **hoofdstuk II** hebben we de interobserver en intraobserver variabiliteit van drie dimensionale gel echografie (3D GIS) bestudeerd bij de beoordeling van intracavitaire afwijkingen (afwijkingen in de holte van de baarmoeder). Vijfenvijftig 3D volumes werden door twee onafhankelijke artsen beoordeeld en één examinator heeft deze beelden tweemaal beoordeeld met een interval van 1 maand. Type, grootte en locatie van de afwijking werden beschreven, evenals de beeldkwaliteit. We vonden een substantiële tot bijna perfecte interobserver en intraobserver overeenkomst voor 3D GIS in het detecteren van de aanwezigheid van een intracavitaire afwijking. De kwaliteit van de 3D volumes werd beoordeeld als matig in 11 van de 45 gevallen. Reproduceerbaarheid nam toe wanneer de kwalitatief slechte beelden werden uitgesloten. We concludeerden dat de reproduceerbaarheid van 3D GIS in de diagnose van intracavitaire afwijkingen zeer goed is.

In **hoofdstuk III** hebben we bekeken of 3D GIS de diagnose en daarmee de preoperatieve planning kan verbeteren (vergeleken met 2D GIS). In een prospectief cohortonderzoek hebben we gekeken of de toevoeging van 3D GIS aan 2D GIS de nauwkeurigheid verhoogt voor de detectie van poliepen en myomen. We waren ook geïnteresseerd of een grotere nauwkeurigheid de planning van hysteroscopische procedures zou verbeteren in termen van benodigde apparatuur en expertise. Bij 110 vrouwen met een vermoedelijk intracavitaire afwijking werden een 2D GIS, een 3D GIS en een hysteroscopie uitgevoerd. Diagnostische nauwkeurigheid werd berekend voor de detectie van poliepen en myomen. We gebruikten zowel histologie als hysteroscopie als referentiestandaard. In vergelijking met 2D GIS is de nauwkeurigheid van 3D GIS beter in het detecteren van poliepen en myomen. Ondanks die verbetering was de planning voor hysteroscopische procedures nauwelijks verbeterd. We concluderen dat in de dagelijkse praktijk de toevoeging van 3D SIS de nauwkeurigheid verbeterde, maar de planning van hysteroscopische procedures amper verbeterde.

In **hoofdstuk IV** beoordelen we systematisch de literatuur die gepubliceerd is over de nauwkeurigheid van 3D SIS. Dertien studies (1053 vrouwen) beschrijven de nauwkeurigheid van 3D SIS voor het detecteren van een focale intracavitaire afwijking waarvan 11 studies (846 vrouwen) geschikt waren voor meta-analyse. Acht studies rapporteerden ook nauwkeurigheid naar type afwijking. De studies waren verricht zoals je dat in de praktijk zou verwachten. Het belangrijkste probleem in de kwaliteitsbeoordeling van de studies was onvoldoende rapportage van de methoden.

Hierdoor was het risico op bias voor verschillende onderdelen onduidelijk. Daarom werd de algemene kwaliteit van het bewijs beschouwd als laag. De sensitiviteit en specificiteit was hoger voor 3D SIS (96.9 % en 99.5%) dan voor 2D SIS (90.9% en 96.3%), dit verschil was echter niet statistisch significant. De nauwkeurigheid is hoger voor 3D SIS dan voor 2D SIS, echter zijn de verbeteringsmarges beperkt, aangezien 2D SIS al zeer nauwkeurig is. We concludeerden dat 3D SIS een alternatief is voor 2D SIS, zolang de juiste technologie en expertise beschikbaar zijn. Zowel 2D SIS als 3D SIS moeten beschouwd worden als een alternatief voor diagnostische hysteroscopie wanneer er een verdenking is op een intracavitaire afwijking, dit geldt voor zowel subfertiele vrouwen als vrouwen met abnormaal menstrueel bloedverlies.

In **hoofdstuk V** richten we ons op 3D echografie zonder toevoeging van een gel of zoutoplossing. De gel en water echo zijn zeer nauwkeurig in de diagnose van submuceuze myomen maar de techniek is invasiever dan conventionele 3D echografie. Daarom hebben we de nauwkeurigheid en betrouwbaarheid van 3D echografie bij het classificeren van submuceuze myomen onderzocht. Een prospectieve pilot studie werd uitgevoerd, onder 14 patiënten die een hysteroscopische myomectomie of ablatie ondergingen (SonataTM). Alle patiënten kregen een echo voorafgaand aan de chirurgische procedure. 2D, 3D, 2D SIS en 3D SIS beelden werden opgeslagen en het percentage uitpuiling in de holte werd gerapporteerd. In deze studie was 3D echografie niet zo accuraat als 2D SIS of 3D SIS bij het beoordelen van het percentage uitpuiling. 3D was niet nauwkeuriger dan 2D in de totale groep. Een matige interobserver overeenkomst voor 3D en een goede interobserver overeenkomst voor 3D SIS werd gevonden. Wat opviel was een grote variatie in beeldkwaliteit tussen de individuele patiënten. In het bijzonder tijdens de luteale fase, wanneer het endometrium goed opgebouwd is, is de zichtbaarheid van de baarmoederholte ten opzichte van de spierlaag verbeterd. Op basis van deze bevindingen concludeerden we dat verfijning van de techniek en timing van 3D echografie bij de evaluatie van myomen moet worden onderzocht voordat evaluatie in grotere studies kan plaats vinden.

In **hoofdstuk VI** hebben we de reproduceerbaarheid geëvalueerd en de waarde van driedimensionale Power Doppler echografie (3D PDUS) bij patiënten met myomen onderzocht. 3D PDUS werd uitgevoerd bij 19 patiënten met myomen en 3D volumes werden beoordeeld door drie onafhankelijke onderzoekers. De volgende parameters werden onderzocht: Vasculaire Index (VI), Flow Index (FI) en Vasculaire Flow Index (VFI) van het myoom, van het kapsel en van een klein gebied met de meeste bloedvaten. Zowel de handmatige als automatische methode werd gebruikt om het volume van een myoom te berekenen en om vervolgens de vaatparameters te berekenen. We vonden dat de handmatige methode voor de VI van het myoom en de VI van het kapsel

de hoogste reproduceerbaarheid hadden (deze was bijna perfect). Beide parameters lijken goede discriminerende eigenschappen te hebben, gezien de grote spreiding van deze waarden tussen de verschillende myomen, onafhankelijk van hun volume. We concludeerden dat de VI beoordeeld met 3D PD reproduceerbaar was in de beoordeling van vascularisatie van myomen.

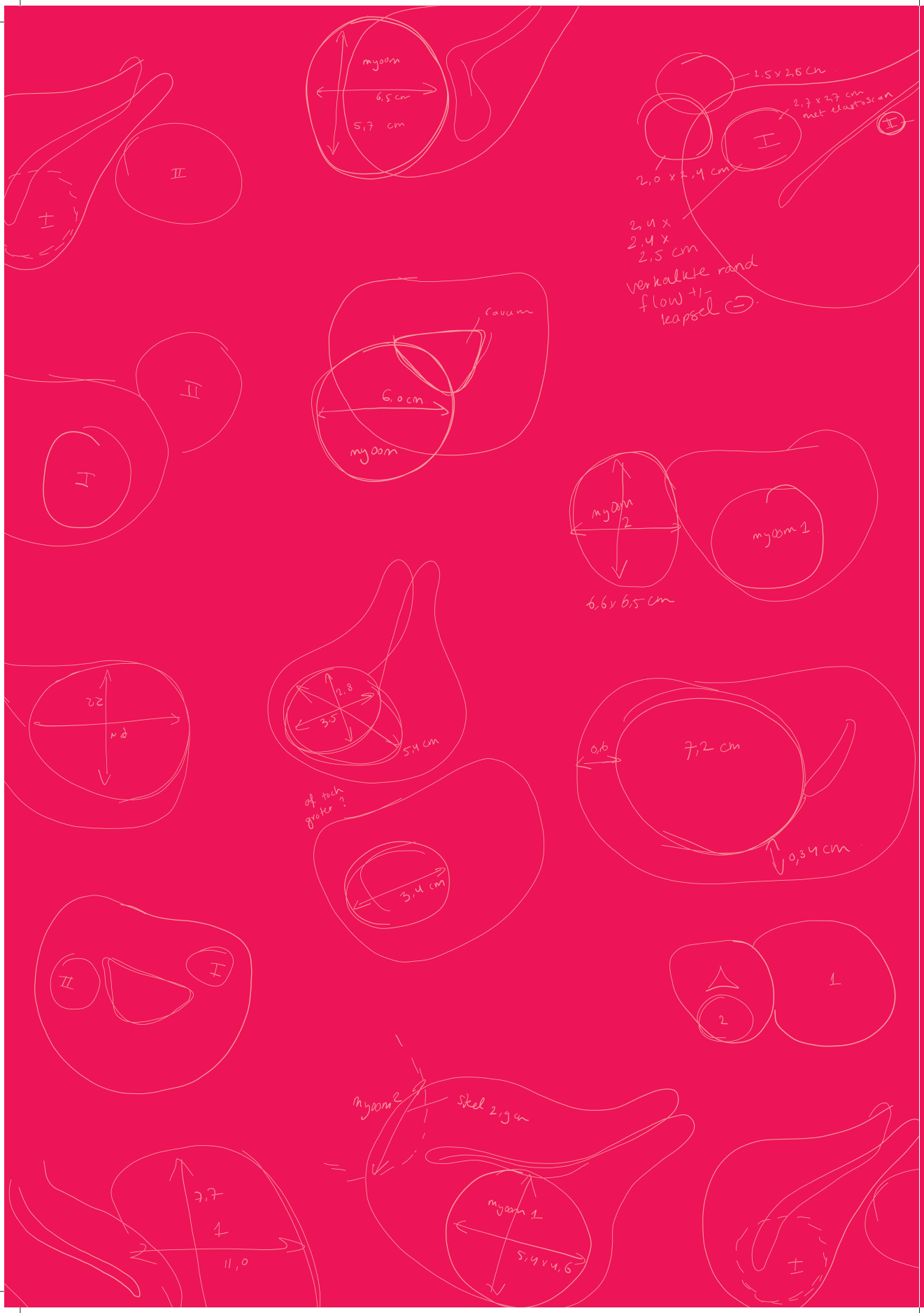
In **hoofdstuk VII** hebben we de invloed van de hartcyclus en verschillende instellingen op een echo apparaat geëvalueerd voor 3D PD in de beoordeling van vascularisatie van myomen. Bij 40 patiënten werd 3D PD uitgevoerd met 3 verschillende instellingen: een vooraf bepaalde instelling (50dB), een hogere gain instelling (65dB) en een individueel gekozen meest optimale instelling. Twee opeenvolgende 3D PD volumes werden genomen om het effect van de hartcyclus te evalueren. Voor de offline metingen heeft één examinator de meest gunstige methode voor volumeberekening en grootte van het kapsel aangegeven. Volumeberekening op handmatige methode had in de meeste gevallen de voorkeur boven de automatische. Een kapsel van 0,5 cm was het meest passend om de vascularisatie van het kapsel van het myoom te berekenen. We vonden dat de vooraf bepaalde instelling het best gebruikt kan worden om de vascularisatie te meten. Door een scan/volume opname van meer dan 10 seconden uit te voeren, lijkt de potentiële invloed van de hartcyclus op de VI beperkt.

Hoofdstuk VIII beschrijft een prospectieve cohortstudie waarbij patiënten met myomen in de loop van de tijd werden gevolgd. Het doel was om vascularisatie van myomen te analyseren, gemeten met 3D Power Doppler, in relatie tot myoom volumeverandering gedurende 12 maanden follow-up. In totaal werden 66 premenopauzale vrouwen gediagnosticeerd met maximaal 2 myomen die kozen voor een expectatief beleid. 3D echografie inclusief Power Doppler werd uitgevoerd bij het eerste bezoek/ op baseline en op 3, 6 en 12 maanden controle. Volume en vasculaire parameters werden berekend met behulp van VOCAL software. Vascularisatie (VI) van het myoom gemeten op baseline was gecorreleerd met het myoom volume op tijdstip 12 maanden ($p = 0,02$). Een toename van 1% in vascularisatie op baseline was geassocieerd met een 7 cm3 groter myoom volume na 12 maanden. We concludeerden dat bij vrouwen met myomen zonder therapie de op baseline gemeten vascularisatie (VI), gemeten met 3D Power Doppler, gecorreleerd is met de absolute myoom volume verandering op 12 maanden.

In **hoofdstuk IX** hebben we de vascularisatie van myomen geëvalueerd in relatie tot symptomen en gezondheid gerelateerde kwaliteit van leven. Een prospectieve cohortstudie werd uitgevoerd onder 53 premenopauzale vrouwen die met maximaal 2 myomen gediagnosticeerd werden. 3D echo inclusief Power Doppler werd uitgevoerd

op baseline (0 maanden) na 3, 6 en 12 maanden follow-up. Deelneemsters werden gevraagd vragenlijsten (PBAC en UFS-QOL) in te vullen over de hoeveelheid bloedverlies tijdens de menstruatie en over symptomen die kunnen voorkomen bij myomen. De vragenlijsten werden op tijdstip 0, 3, 6 en 12 maanden follow-up ingevuld. We vonden dat de baseline vascularisatie (VI) geassocieerd was met toename van bloedingsklachten (PBAC score). Als we corrigeren voor het myoom volume bij aanvang dan is de gevonden associatie niet meer significant. Andere factoren zoals aantal myomen waren niet van invloed. Subgroepenanalyses voor type myoom (submuceus, intramuraal en subserosaal) toonden een statistisch significante associatie tussen baseline VI en PBAC score op 12 maanden follow-up voor intramurale myomen. We concludeerden dat de studie liet zien dat zowel vascularisatie als myoom volume geassocieerd zijn met een toename van bloedingsklachten en symptomen gerelateerd aan myomen en de kwaliteit van leven. Vascularisatie (VI) kan ons in de toekomst wellicht helpen om te voorspellen welke (intramurale) myomen in de loop van de tijd meer klachten zullen geven.

In **hoofdstuk X** worden de gevonden resultaten en toekomstige onderzoeksperspectieven bediscussieerd. We hebben aangetoond dat 3D GIS goed reproduceerbaar is om intracavitaire afwijkingen op te sporen. 3D SIS is nauwkeuriger dan 2D SIS, maar de marges van verbetering zijn beperkt, omdat 2D SIS al zeer nauwkeurig is. Momenteel lijkt de klinische relevantie beperkt. Het gebruik van 3D echografie zonder contrast bij het classificeren van myomen is haalbaar maar moet nog verbeterd worden voordat zijn waarde in het diagnostische proces kan worden bepaald in toekomstige studies. 3D power Doppler is uitvoerbaar en accuraat voor de beoordeling van vascularisatie van myomen. De vasculaire index (VI) is reproduceerbaar in myomen en is gerelateerd aan volume verandering over 12 maanden bij vrouwen zonder therapie. Vascularisatie kan ons ook helpen om de toename van symptomen te voorspellen. Toekomstig onderzoek is nodig om te bepalen wat de beste methode is om vascularisatie te kwantificeren en om het behandelingseffect te beoordelen. Wellicht kan het ook gebruikt worden om te differentiëren tussen myomen en sarcomen.


myoom
6,5 cm
5,7 cm
II
I
1,5 x 2,6 cm
2,7 x 2,7 cm
met elastoscan
I
2,0 x 1,4 cm
2,4 x
2,4 x
2,5 cm
verkalkte rand
flow +/-
kapsel
vacuum
6,0 cm
myoom
II
I
myoom
2
myoom 1
6,6 x 6,5 cm
2,2
2,8
3,5
5,4 cm
of toch
groter ?
3,4 cm
0,6
7,2 cm
0,34 cm
II
I
1
2
myoom 2
steel 2,9 cm
7,7
1
11,0
myoom 1
5,4 x 4,6
I

12

Appendices

LIST OF CO AUTHORS

M.W. van Baal, Department of Obstetrics and Gynaecology, Flevo Ziekenhuis, Almere, the Netherlands

H.E. Betjes, Department of Obstetrics and Gynaecology, VU University medical centre (VUmc), Amsterdam, the Netherlands

M.A. BijderVaate, Department of Obstetrics and Gynaecology, VU University medical centre (VUmc), Amsterdam, the Netherlands

H.A.M. Brölmann, Department of Obstetrics and Gynaecology, VU University medical centre (VUmc), Amsterdam, the Netherlands

T.J. Clark, Department of Obstetrics and Gynaecology, Birmingham Women's Hospital, Birmingham, United Kingdom

W.J.K. Hehenkamp, Department of Obstetrics and Gynaecology, VU University medical centre (VUmc), Amsterdam, the Netherlands

M.W. Heymans, Department of Epidemiology and Biostatistics, VU University medical centre (VUmc), Amsterdam, the Netherlands

J.A.F. Huirne, Department of Obstetrics and Gynaecology, VU University medical centre (VUmc), Amsterdam, the Netherlands

A.L. Keizer, Department of Obstetrics and Gynaecology, VU University medical centre (VUmc), Amsterdam, the Netherlands

B.W.J. Mol, Discipline of Obstetrics and Gynaecology, School of Medicine, Robinson Research Institute, The University of Adelaide, Adelaide, Australia

S. Stoelinga, Department of Obstetrics and Gynaecology, VU University medical centre (VUmc), Amsterdam, the Netherlands

J.W.R. Twisk, Department of Epidemiology and Biostatistics, VU University medical centre (VUmc), Amsterdam, the Netherlands

LIST OF PUBLICATIONS

Viviënne E.B. Lamberti, **Lotte L. Nieuwenhuis**, Flora Vernooij. Oxytocine staken in de actieve fase van de bevalling? NTOG najaar 2017.

Keizer AL, **Nieuwenhuis LL**, Hehenkamp WJK, Twisk JWR, Brölmann HAM, Huirne JAF. Fibroid vascularisation assessed with 3D power Doppler as predictor for fibroid related symptoms and quality of life; a prospective cohort study. Submitted BJOG august 2017.

Keizer AL, **Nieuwenhuis LL**, Twisk JWR, Huirne JAF, Hehenkamp WJK, Brölmann HAM. Role of 3-Dimensional Sonography in the Assessment of Submucous Fibroids: A Pilot Study. J Ultrasound Med. 2017 Aug 4. doi: 10.1002/jum.14331.

L.L. Nieuwenhuis, W.J.K. Hehenkamp, H.A.M. Brölmann, J.A.F.Huirne. 3D Power Doppler in uterine fibroids; influence of gain, cardiac cycle and off-line measurement techniques. J Obstet Gynaecol. 2017. DOI:10.1080/01443615.2017.1330323.

Nieuwenhuis LL, Hermans FJ, Bij de Vaate AJM, Leeflang MM, Brölmann HA, Hehenkamp WJ, Mol BWJ, Clark TJ, Huirne JA. Three-dimensional saline infusion sonography compared to Two dimensional saline infusion sonography for the diagnosis of focal intracavitary lesions. Cochrane Database Syst Rev. 2017 May 5;5:CD011126.

Nieuwenhuis LL, Keizer AL, Stoelinga B, Twisk J, Hehenkamp W, Brölmann H, Huirne J. Fibroid vascularisation assessed with three-dimensional power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective cohort study. BJOG. 2017 Feb 17. doi: 10.1111/1471 0528.14608.

Nieuwenhuis LL, Betjes HE, Hehenkamp WJ, Heymans MW, Brolmann HA, Huirne JA. The use of 3D power Doppler ultrasound in the quantification of blood vessels in uterine fibroids: feasibility and reproducibility. J Clin Ultrasound. 2015 Mar;43(3):171-8. doi: 10.1002/jcu.22208. Epub 2014 Aug 11.

Nieuwenhuis LL, Bij de Vaate MA, Hehenkamp WJ, Heymans MW, van Baal MW, Brölmann HA, Huirne JA. Reproducibility of three-dimensional gel installation sonohysterography in the assessment and classification of intrauterine abnormalities. Eur J Obstet Gynecol Reprod Biol. 2014 Aug;179:141-6. doi: 10.1016/j.ejogrb.2014.05.010. Epub 2014 May 22.

Nieuwenhuis LL, de Vaate MA, Hehenkamp WJ, Heymans MW, van Baal MW, Brölmann HA, Huirne JA. Diagnostic and clinical value of 3D gel installation sonohysterography in addition to 2D gel installation sonohysterography in the assessment of intrauterine abnormalities. Eur J Obstet Gynecol Reprod Biol. 2014 Apr;175:67-74. doi: 10.1016/j.ejogrb.2014.01.015. Epub 2014 Jan 30.

Kappers I, Vollebergh MA, van Tinteren H, Korse CM, **Nieuwenhuis LL**, Bonfrer JM, Klomp HM, van Zandwijk N, van den Heuvel MM. Soluble epidermal growth factor receptor (sEGFR) and carcinoembryonic antigen (CEA) concentration in patients with non-small cell lung cancer: correlation with survival after erlotinib and gefitinib treatment. Ecancermedicalscience. 2010;4:178. doi:10.3332/ecancer.2010.178. Epub 2010 Nov 3.

Wouters MW, van Geel AN, **Nieuwenhuis L**, van Tinteren H, Verhoef C, van Coevorden F, Klomp HM. Outcome after surgical resections of recurrent chest wall sarcomas. J Clin Oncol. 2008 Nov 1;26(31):5113-8. doi: 10.1200/JCO.2008.17.4631. Epub 2008 Sep 15.

PHD PORTFOLIO

PhD Training

2014 Course Endnote
2014 Course in statistics: Longitudinal data-analyse
2013 Cochrane: systematic review of diagnostic test accuracy
2013 Course in statistics: Introduction biostatistics and clinical epidemiology
2011 Cochrane: preparing protocol of diagnostic test accuracy
2011 Course Pubmed

Presentations

2017 Doelencongres Rotterdam. Voordracht '3D Power Doppler vascularisatie als voorspeller van groei'
2015 ISUOG Montreal. Voordracht 1: '3D PD as predictor for uterine fibroid growth' Voordracht 2 '3D PD in uterine fibroids; influence of gain, cardiac cycle and offline measurements techniques'
2015 ESGE Budapest. Voordracht 'results from a Cochrane review on 3D SIS for the diagnosis of focal intracavitary lesions'
2015 Doelencongres Rotterdam. Voordracht 'toegevoegde waarde van 3D GIS aan 2D GIS bij intracavitaire afwijkingen'
2014 ISUOG Barcelona. Voordracht 'The use of 3D power Doppler ultrasound in the quantification of blood vessels in uterine fibroids'
2013 ICaR-VU Colloquium, Amsterdam juni 2013. 3D Power Doppler in fibroids
2013 Latest trends and approach in ultrasound Kiev. Voordracht 3D echo en Elastografie
2012 ESGE Parijs. Voordracht Toegevoegde waarde 3D GIS

General education

Monthly

- Research meeting with the subdivision benign gynaecology VUmc
- Research lunch with all PhD candidates in obstetrics and gynaecology VUmc
- Mentoring several final year students in their scientific internship

Annually

- Research conference of the department of obstetrics and gynaecology VUmc
- Reviewing several manuscripts for gynaecology journals

DANKWOORD

'Ze kennen niet van je winnen, maar je ken wel van ze verliezen' - Johan Cruijff

'Informatie is geen inzicht, een mening geen kennis' - Ivan Wolffers

Wat een voorrecht om te mogen promoveren. En wat ben ik trots op het eindresultaat. Dit proefschrift had niet tot stand kunnen komen zonder de steun en hulp van vele personen die ik dan ook graag wil bedanken.

Promotoren en co-promotoren

Prof. Dr. Huirne, lieve Judith, na onze eerste kennismaking was ik meteen dolenthousiast, wat heerlijk dat jij 7 dingen tegelijk kan bespreken. Als Barbara en ik het nut van ons onderzoek even kwijt waren en klaar waren voor submissie in de Donald Duck, dan vroeg ik me na een bezoek bij jou altijd af waarom de Lancet eigenlijk nog niet had gebeld met het verzoek ons stuk te mogen publiceren. Ik heb bewondering voor jou onhoudbaar enthousiasme voor wetenschap en dit proefschrift is slechts een klein onderdeel in de grote lijnen die je voor ogen hebt. Je bent een onuitputtelijke bron van kennis en hebt tomeloze energie en miljarden ideeën voor verder onderzoek. Je bent een echte motivator, enorm veel dank voor eigenlijk alles!

Prof. Dr. Brölmann, Ha Hans, een echte professor, een simpel ja of nee krijg je niet maar je maakt graag tijd om ergens eens goed over na te denken of je kennis en hypothesen te delen. Een van mijn eerste herinneringen aan jou is op weg naar een etentje met alle onderzoekers. Terwijl iedereen inhield voor rood licht en wij in de eerste instantie ook (ik kon toch zeker niet door rood rijden naast de prof), reden we uiteindelijk wel degelijk door rood. Je moest wel in Amsterdam zijn opgegroeid en het ijs was gebroken. Ik wil je bedanken voor je waardevolle en tegelijkertijd vooral zeer grappig commentaar op de stukken. Ik zal geen voorbeeld geven maar het resulteerde naast hardop lachen achter mijn PC ook voor de nodige inhoudelijke verbetering.

Dr. Hehenkamp, beste Wouter, jij zorgde aan de zijlijn vooral voor de rust en ontspannen houding. Je commentaar als 'lijkt me prima, submit maar' waren soms een nodige verademing zonder dat dit ten koste ging van de nodige kritische noot op kwaliteit van onderzoek. Dank voor je positieve benadering en de gezelligheid en etentjes op congressen.

Dr. van Baal, beste Marchien, jij was degene die mij promootte bij Judith nadat ik had aangegeven graag te willen promoveren. Ik heb mijn start in het Flevo als ontzettend leuk en leerzaam ervaren. Dank voor je steun en begeleiding in die periode.

Promotiecommissie/Leescommissie
Geachte Prof. Dr. M.Y. Bongers, Dr. P.M.A.J. Geomini, Prof. Dr. C.B. Lambalk, Prof. Dr. F.W. Jansen, Prof. Dr. J.W.R. Twisk, Dr. T. van den Bosch. Ik wil u allen graag hartelijk bedanken voor uw tijd en moeite voor het beoordelen van mijn proefschrift en de oppositie tijdens mijn verdediging. Prof. T.J. Clark, I would like to thank you for taking the time and effort to review my dissertation and taking place in the opposition during my defence.

Patiënten
Alle vrouwen van de myoompoli en alle vrouwen die mee hebben gedaan aan de onderzoeken. Ondanks kinderen en een drukke baan kwamen ze soms speciaal voor een van de onderzoeken naar het VUmc. Dank voor jullie interesse in de studie(resultaten) en vaak ook nog in mij persoonlijk. Veel dank voor jullie inzet om de zorg voor vrouwen te verbeteren!!

Michel Wouters wil ik graag noemen voor het aanwakkeren van mijn enthousiasme voor het doen van wetenschappelijk onderzoek. Als 4e-jaars student stuurde ik een email naar alle specialisten in het Antonie van Leeuwenhoek ziekenhuis omdat oncologie mijn interesse heeft. Jij reageerde direct en dankzij jouw begeleiding en enthousiasme kwam er een mooie publicatie, congresvoordracht en prijs voort uit een wetenschappelijke stage. Veel dank daarvoor!

VUmc collega's
Ik wil graag alle collega's in het VUmc bedanken die hebben geholpen aan de totstandkoming van dit proefschrift.

En in het speciaal Ted Korsen voor de hulp met patiënten bellen, uitleggen hoe een vragenlijst in te vullen, etc etc. De poli assistenten voor de hulp met inplannen van echo's, de echoscopisten voor ergonomische tips, Ivan Palmer, tja, zonder PC kan je niets, jouw rol is dus duidelijk. Studenten Kiko Demissi en Charlotte Nikkels voor het helpen met invullen van de database in hun vrije tijd.

Dr. Leeflang, beste Mariska, gelukkig had ik jou aan mijn zijde voor deze DTA review anders was de meta-analyse nooit gelukt. Dank voor je uitleg, geduld en hulp bij deze bevalling!

Prof. Dr. Twisk, beste Jos, het licht aan het einde van de statistiek tunnel! Je was altijd bereikbaar, begreep precies wat ik bedoelde en je was altijd bereid om te helpen. Je bent een enorme motivator voor mij geweest.

Mede onderzoeksters
Machteld, Debbie, Margot, Barbara, Anke, Ilse, Kim, Marit, Mirte, Joukje, Lisette, Maaike, Viola, Roos, Marjolein, Nicole, Eva, Yoav, Daphne, Ton, Eva, Anouk, Jorine, Annefleur en Inge. Wat had ik graag fulltime bij jullie gezeten en wat was het gezellig op en buiten de onderzoekerskamer. Dank allemaal voor de tips en steun!

In het bijzonder wil ik Barbara nog even noemen. Bar, je bent zo heerlijk relaxed en lijkt je soms nergens druk om te maken. Congres met jou betekent naast de congreshal ook de winkels, het strand, de terrasjes en de restaurantjes van een stad bezoeken. En wat vond ik het fijn om samen met jou te zeuren over ons onderzoek. Eigenlijk zou jouw boekje hier ook moeten liggen. Laten we als jij gaat promoveren alsnog een symposium in combinatie organiseren. Gewoon omdat het kan!

Collega's Flevo
Ik wil graag alle collega's in het Flevo ziekenhuis bedanken voor de warme en leuke start als dokter, in het bijzonder Marchien en Gunilla voor het vertrouwen. De mede A(N) IOSSEN, zaalarts-baalarts en andere positivos maakten de baan zo leuk.

Collega's Spaarne
Opeens AIOS in een ander ziekenhuis. Ik wil ook daar alle collega's bedanken voor de leuke en leerzame start van mijn opleiding en steun om het proefschrift af te maken! Al vanaf de eerste autorit met Nicole zat de sfeer er altijd goed in.

Familie
Dank voor alle gezellige borrels, feesten en partijen waar jullie altijd geïnteresseerd waren in mijn proefschrift!

Schoonfamilie
Je moet maar geluk hebben met je schoonfamilie en wat heb ik het enorm getroffen. Dank voor alle gezelligheid en warmte!

Vrienden
Ik kan jullie niet op één hoop gooien maar onmogelijk allemaal apart beschrijven. Ieder van jullie is op z'n eigen manier dierbaar voor mij. Oude vrienden, nieuwe vrienden, senaatsgenoten, dispuutsgenoten, huisgenoten, sportgenoten, zonder jullie had dit

proefschrift hier ook niet gelegen. Van jullie krijg ik enkel positieve energie, ik had me geen betere vrienden kunnen wensen! Ik wil jullie bedanken voor het aan luisteren van mijn gezeur, jullie interesse en bovenal humor en warmte.

Paranimfen
Josefine, lieve Joos, als een van mijn oudste en slimste vriendinnen hoor jij op z'n dag naast mij te staan. Jouw eerlijkheid en al meer dan 30 jaar vriendschap waardeer ik enorm.

Sabien, lieve Bien, tijdens onze studie was er weinig waar we niet beide (midden)in zaten. Je bent een Uber dokter en lijkt onverwoestbaar. Ik ben trots dat ik je getuige mocht zijn, logisch dat jij vandaag naast mij staat.

Ouders
Lieve pap en mams, dat ik met jullie als ouders bof is niet alleen mijn mening. Jullie laten mij mijn eigen keuzes maken en bezitten over een dosis vertrouwen in mij wat als oneindig voelt. Jullie aanmoediging en steun is altijd onvoorwaardelijk aanwezig. Daarvoor ben ik jullie enorm dankbaar. Zonder jullie zou onder andere dit proefschrift hier niet liggen!

Pieter
Destijds de allerleukste barman van Amsterdam. We kennen elkaar bijna 3 jaar en je bent al niet meer weg te denken. Je begreep eigenlijk maar weinig van al dat gesubmit maar toonde altijd interesse. Je bent een perfecte afleiding en tegenhanger van al het geneeskundige en alleen al je aanwezigheid is soms genoeg. Ik heb ontzettend veel zin in de rest van ons leven en ben heel blij dat jij de papa van mijn kind(eren) wordt.

CURRICULUM VITAE

Lotte Lisa Nieuwenhuis werd op 15 januari 1983 geboren in Maputo (Mozambique) waar haar ouders beide werkzaam waren in het onderwijs. Op 2-jarige leeftijd keerde zij terug naar Nederland en ging wonen in de geboortestad van haar vader, Amsterdam. In 2001 behaalde zij haar VWO-diploma profiel natuur en gezondheid aan het Montessori Lyceum Amsterdam. Zij koos ervoor niet te starten met de studie geneeskunde maar eerst een jaar (vooral) te reizen. In 2002 startte zij met de studie geneeskunde aan de Universiteit van Amsterdam/ het Academisch Medisch Centrum. Haar wetenschappelijke stage verrichtte zij in het Antonie van Leeuwenhoek ziekenhuis bij de oncologische chirurgie. Ze deed onderzoek naar sarcomen en de interesse voor wetenschappelijk onderzoek was gewekt. Ze won een scriptieprijs voor studenten die onderzoek verrichten naar kanker en een eerste publicatie volgde. Na een jaar fulltime in het bestuur van een studentenvereniging te hebben gezeten en opnieuw het nodige reizen na een keuze co-schap in Argentinië studeerde zij in 2010 af als arts. Hierna startte zij haar eerste baan als dokter, gedurende een maand, bij de urologie in het Rijnland ziekenhuis onder de vleugels van drs. Z.W. Sneller en dr. P.D.J. Vegt om vervolgens als anios gynaecologie en verloskunde te starten in het Flevoziekenhuis in Almere (opleiders dr. G. Kleiverda en dr. W.M. van Baal). Naast haar baan als anios verrichtte zij promotieonderzoek onder begeleiding van Prof dr. H.A.M. Brölmann, Prof dr. J.A.F. Huirne en dr. W.J.K. Hehenkamp wat heeft geleid tot dit proefschrift. In 2015 is zij met veel enthousiasme gestart aan de opleiding tot gynaecoloog, allereerst in het Spaarne Gasthuis (opleider dr. A. Vollebregt) in Hoofddorp en vanaf juli 2017 in het VU medisch centrum (Prof. Dr. J.I.P. de Vries).